THE RESPONSE OF THE HEPATIC ARTERY BLOOD
FLOW TO THE INTRA-CELIAC INFUSION OF
VASOPRESSIN AS MONITORED
WITH ELECTROMAGNETIC FLOW PROBES

Richard Jay Fingeroth

1973

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Richard Jay Fingeroth

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May 8, 1973

Date

THE RESPONSE OF THE HEPATIC ARTERY BLOOD FLOW

TO THE INTRA-CELIAC INFUSION OF VASOPRESSIN

AS MONITORED WITH ELECTROMAGNETIC FLOW PROBES

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PURPOSE

As with most new procedures, the intra-arterial infusion of vasopressin for the control of gastro-intestinal bleeding does entail certain risks. Among these has been the fear that hepatic ischemia may result secondary to decreased hepatic artery blood flow if the hepatic artery were to be directly exposed to vasopressin during celiac axis or superior mesenteric artery infusions. (9;106;132;173)

Using the dog as my experimental model I have studied the changes in blood flow through the hepatic artery with non-cannulating electromagnetic flow probes during the direct intra-celiac infusion of vasopressin. I then examined the pre- and post-infusion angiograms of patients who underwent therapeutic intra-celiac vasopressin infusion for gastro-intestinal bleeding at the West Haven Veterans' Administration Hospital to correlate the results which I found in the laboratory in dogs with actual clinical observations in man.

INTRODUCTION

In order to fully understand both my laboratory work and its clinical significance it would be useful for the reader to be knowledgeable about vasopressin, the hepatic vasculature, and angiography, as well as having a clear understanding of the pertinent experiments which comprise the background against which my results must be interpreted and evaluated. I have attempted to provide this information in the following sections.

VASOPRESSIN

Vasopressin is synthesized in cell bodies in the paraventricular and supraoptic nuclei of the hypothalamus and migrates along the axons of these nerve cells to be stored as neurosecretory granules in the nerve cell endings near perivascular spaces in the neurohypophysis, which is part of the posterior lobe of the pituitary gland formed as a downward growth from the floor of the diencephalon. Oxytocin, which causes contraction of uterine muscle and contraction of myoepithelial cells in the alveoli of mammary glands is also synthesized and stored by an identical hypothalamoposterior hypophyseal system. (19;45) The control of

vasopressin release is mediated through osmoreceptors (increased plasma osmolarity leads to increased vasopressin release),(95) volume receptors (increased plasma volume leads to decreased vasopressin release), (76) as well as by emotional and physical stress. (95)

Oliver first demonstrated the pressor effect of pituitary extract in 1895, noting that intravenous infusion of the extract caused a rise in blood pressure and that perfusion of the extract through the vascular system of a pithed frog greatly decreased the flow of fluid. (137) In 1928, Kamm separated two active principles from the posterior pituitary; one was a pure pressor principle eighty times as potent as the International Standard of Powdered Pituitary and the other was a pure oxytocic principle. He found the pressor principle to also be responsible for the anti-diuretic action of pituitary extract (96) which had first been described by von den Velden in 1913. (190) In 1953, DuVigneaud identified and synthesized arginine-8-vasopressin (62) which is the natural ocurring hormone in all mammals except for the pig and the hippopotamus, where arginine in the side chain is replaced by lysine to form lysine vasopressin. The vasopressins are all cyclic octapeptides with a closed ring of five amino acids and a side chain of three amino acids. (182) The chemical activity of the compound depends on both the cyclic pentapeptide and the tripeptide side chain; thus, opening of the circle or

removal of the terminal glycine amine group (by trypsin, for example) rapidly inactivates the vasopressin. (76)

The third common type of vasopressin available in addition to the lysine-8-vasopressin and arginine-8-vasopressin is phenylalanine-lysine-vasopressin (PLV-2) a synthetic compound formed by substituting phenylalanine for tyrosine in position two of lysine vasopressin. Phenylalanine-lysine-vasopressin has been found to have the same pressor effect as the natural occurring vasopressins, but anywhere from 1/2 to 1/70 their anti-diuretic effect; PLV-2 is, therefore, felt to have a selective pressor effect. (15;182) Lysine and arginine vasopressins have equivalent pressor and anti-diuretic effects when compared with each other.

Although we are mainly concerned with the effect of vasopressin on the gastro-intestinal vasculature, we should briefly review some of its other properties. The main effect of vasopressin is to control the reabsorption of free water from the collecting tubules of the kidney. This is achieved by vasopressin doses many hundreds of times smaller than those doses required to produce a pressor response (47), and it is probably the only true physiologic function of vasopressin in mammals. (76) In pharmacologic doses, however, vasopressin has many additional effects. In 1930, Gruber and Kountz, and in 1961, Drapanas, found that vaso-

pressin caused constriction of the coronary arteries (26;

53;85) in addition to a decreased heart rate and increased

systemic arterial blood pressure. The fall in heart rate

was only partially prevented by severing of the vagi or

administration of atropine and, therefore, it was felt to

be due to both a parasympathetic response to the increased

blood pressure as well as a direct depressive effect of

vasopressin on the myocardium. (85) Vasopressin was also

noted to cause Cheynes-Stokes respirations in unanesthetized

dogs. (84) Vasopressin is known to decrease the basal

metabolism rate, cardiac oxygen consumption, and the car-

diac output in mammals. (46;50;53;63;71;187) The decrease

in cardiac output is associated with a decrease in cardiac

work and is probably due to a direct depressive effect of

vasopressin on the myocardium in addition to the decrease

in coronary blood flow and the reflex bradycardia. (63)

In 1898, Von Cyan first reported pulsus bigeminus in ani-

mals injected with pituitary extract (85); since then vaso-

pressin has been noted to cause several EKG changes includ-

ing prolonged P-R interval, sino-atrial block, non-specific

ST-T wave changes, and various irregular rhythms. (155)

Ruskin has suggested using vasopressin as a test to bring

out latent coronary vascular insufficiency; using anginal

pain following vasopressin injection as his end point he ob-

tained results which correlated well with the Master's ex-

ercise test. (155) In 1936, Collins and Root reported on

the use of vasopressin to eliminate intestinal gas during

cholecystography; vasopressin (5-20 Units) increased the

peristaltic activity and propulsive movement of the bowel.

(76) There have been reports, however, of patients with no

known EKG or clinical history of cardiac disease who have

suffered acute and fatal myocardial infarctions during this

procedure. (124;172) Dearing and Essex in 1944, by repeat-

ed injections of vasopressin in cats, were able to produce

focal histologic changes in the myocardium, most prominent

in the sub-endocardial layers of muscle of the left ventricle,

associated with significant EKG changes. (124) Due to its

effect on gastro-intestinal motility vasopressin has also

been used to relieve intestinal distention. (26) Vasopressin

also reduces the volume of salivary, biliary and pancreatic

juices (157) as well as reducing the volume of histamine,

insulin, and food stimulated gastric secretions. (109;152;

158;159) An initial and transient increase in blood flow

through cutaneous vessels, secondary to increased systemic

blood pressure and active vasodilatation of the vessels,

is followed by a prolonged cutaneous vasoconstriction during

vasopressin infusions. (35;192) Local infiltrations of

vasopressin have been used in plastic, dental and cervical

surgery to both prolong the effects of local anesthetics

and to provide a bloodless field (104;140;168); vasopressin

was found to be superior to adrenaline for this purpose
in that vasopressin produced pallor without the central
cyanosis that was seen with adrenaline; it is therefore
felt that adrenaline causes more tissue damage and necrosis
with poorer healing. (100) Vasopressin has been found to
exert a direct effect on the thyroid gland indentical with
that of appropriate doses of TSH (69) as well as causing an
increase in the level of serum cortisol felt to be medi-
ated via the release of ACTH and not to be a direct effect
on the adrenal cortex. (110;128) Both of these effects are
only seen with exogenous pharmacologic levels of vasopressin.
Vasopressin has also been found to protect pancreatic blood
flow during experimental acute pancreatitis; when vasopressin
was not given, pancreatic flow decreased by 40-60% but with
vasopressin the pancreatic flow remained stable. This was
attributed to the maintenance of good aortic perfusion pressure
and to a redistribution of arterial flow within the pancreas
to the areas of inflammation. (144) Finally, many of the above
mentioned actions of vasopressin are manifested clinically
during vasopressin infusions by skin pallor, abdominal cramps,
nausea, bowel movements, and urgent micurition followed
by several hours of anti-diuresis. (151;166;182)

Vasopressin, in pharmacologic doses, also has signi-
ficant effects upon the gastro-intestinal and hepatic vas-
cular systems which make it useful in the treatment of

gastro-intestinal bleeds from both arterial and variceal sources. It is known that vasopressin causes peripheral vasoconstriction with a decrease in blood flow in the muscular arteries of the body, such as the branches of the femoral artery. (187) A similar effect is seen in the arteries supplying the gastro-intestinal system. Vasopressin has been shown to decrease the blood flow through the superior mesenteric artery by approximately 60%, (3;5;6;37;50;53; 83;87;106;134;135;142;165) to decrease the inferior mesenteric artery blood flow by equivalent amounts, (3;83;135; 165) to decrease the splenic artery blood flow, (3;37;82; 83;135;165) and to decrease the gastric artery blood flow by 20% to 70%. (3;14;25;50;135;142) The effect of vasopressin on the hepatic artery blood flow has been less clear, with several investigators reporting an increase in hepatic artery blood flow (3;37;63;83;87;90;135;141;169) while others report an increase in hepatic artery pressure and a decrease in hepatic artery blood flow as is seen in the rest of the systemic arteries in the body, (53;98;117;165) and still others report an inconsistent response of the hepatic artery to vasopressin. (142) I will discuss all of these experiments involving the hepatic artery in detail at the end of the introduction since they are directly related to my research.

Vasopressin has also been found to be very effective

in lowering portal venous pressure in experimental animals
as well as in man. (48;53;56;58;62;83;90;98;141;149;165;
166;170;178;182) The predominant feeling is that this
effect is secondary to a decrease in splenic, gastric, super-
ior mesenteric and inferior mesenteric arterial blood flow
secondary to vasoconstriction in these vessels so that as
a result less blood is reaching the portal vein and thus
a "medical" portal shunt is created; ie., the main effect
of vasopressin on the portal vein seems to be pre-portal.
(3;32;36;57;83;97;134;142;169;178) Several investigators,
however, have claimed to demonstrate an additional direct
response of the portal vein to vasopressin. (59;120;135;
169)

It is because of its arterial vasoconstrictive effects
and its ability to reduce portal venous pressure that vaso-
pressin has become a clinical tool in the treatment of
gastro-intestinal bleeding. Vasopressin was first used to
control hemorrhage during the first half of the twentieth
century when it was used in intravenous doses of 10 units
in a ten minute infusion to treat brisk hemoptysis secondary
to bronchiectasis, tuberculosis, tumors, fungal diseases
and so on. (181) The results were rather good, giving the
clinician time to determine and treat the primary cause of
the bleeding. Nevertheless, for reasons which are not
perfectly clear this procedure is no longer used in the

treatment of severe hemoptysis. In 1955, Kehne reported on
the successful use of intravenous vasopressin in the treat-
ment of two patients with cirrhosis who were bleeding from
esophageal varices. In both cases the bleeding was well con-
trolled; the first patient re-bled five times over the next
six months, responding well to vasopressin each time, and
the second patient underwent excision of his varices and did
well post-operatively. (98) There have been many other reports
on the use of vasopressin in the control of hematemesis from
esophageal varices since Kehne's original work. (43;122;132;
133;153;162;166;182) It is felt by the above researchers that
vasopressin controls the bleeding by reducing the portal venous
pressure, thus either stopping, or at least decreasing the
flow of blood through the esophageal varices so that a clot is
able to form over the bleeding site. A possible additional
mechanism, suggested by Aronsen, is that vasopressin actually
causes constriction of the lower esophageal musculature. He
created portal hypertension in dogs by ligating the portal vein;
fourteen of the animals developed porto-systemic communications
in the form of para-esophageal and submucosal esophageal var-
ices. During intravenous vasopressin infusion it was noted
by angiography that the submucosal esophageal varices dis-
appeared but the para-esophageal collaterals dilated; it was
felt that this response was due to the contractile effect

of vasopressin on the smooth muscle of the esophageal wall,
closing off the feeding and draining radicles of the sub-
mucosal varices as they passed through the esophageal mus-
culature and thereby causing more blood to flow through the
para esophageal collaterals. (3)

More recently Baum and Nusbaum, who were working with
selective angiography to diagnose sites of gastro-intestinal
bleeding (see angiography) infused vasopressin intra-
arterially through the catheter which they had used for the
angiographic demonstration of the bleeding site and which
was still positioned in the bleeding vessel. They found
that the direct infusion of vasopressin into a bleeding artery
within the gastro-intestinal system led to cessation of
bleeding from that vessel secondary to vasoconstriction and
decreased blood flow, which then allowed the normal coagu-
lation factors to function. They have successfully infused
vasopressin into the superior mesenteric artery to control
bleeding esophageal varices as well as small bowel ulcers.
They have also infused vasopressin into the gastric artery
to control Mallory Weiss tears, hemorrhagic gastritis and
bleeding gastric ulcers; into the gastroduodenal artery to
control bleeding duodenal ulcers, and into the hepatic artery
to control a bleeding hepatoma. (9;11;47;130;132;133) Baum
and Nusbaum have also used vasopressin intra-operatively
to control blood loss during porta-caval shunt surgery. (9)

In general they have been able to control most bleeds where it was possible to infuse the vasopressin directly into the vessel which was bleeding, proximal to the site of bleeding. Vasopressin will not control bleeding secondary to erosion of the main stem of a major vessel; it is most effective when the bleeding site is from a peripheral branch of the artery since vasopressin is best at producing peripheral vasoconstriction. Baum and Nusbaum usually infuse vasopressin (Pitressin) at a dosage rate of 0.1-0.2 Pressor Units/cc./minute; at these rates they claim to see no tachyphylaxis and only minimal cardiac and renal effects since most of the infused vasopressin is rapidly inactivated in the portal system. By infusing directly proximal to the bleeding site they are able to use much smaller doses than would be necessary with intravenous infusions. (191)

Both Rosch and Meves, in different laboratories, infuse vasopressin into the superior mesenteric artery to control bleeding esophageal varices. However, for arterial gastrointestinal bleeds they use epinephrine with propanolal in spite of the frequent occurrence of re-bound bleeding after the epinephrine infusions. (122;153) In comparing the vasopressin infusions with the epinephrine infusions Rosch found basically equivalent vasoconstrictor properties in the mesenteric arteries, but post infusion blood flow in the epinephrine treated vessel was 145% of pre-infusion level for

three minutes while blood flow in the vasopressin treated
vessel was still only 80% of pre-infusion level forty minutes
after the infusion was ended. (154)

Intra-arterial infusion of vasopressin is also being
used to control bleeding from non-gastro-intestinal sites.
Slezak reported infusing vasopressin into the internal iliac
artery of a patient who was bleeding from a branch of that
vessel which had been eroded away by carcinoma. He hypothe-
sized that in addition to the vasoconstrictive effect of vaso-
pressin, small clots may have embolized from the tip of the
catheter and moved distally to occlude the bleeding site.
He also emphasized the importance of careful fluid balance
plus EKG and CVP monitoring to guard against cardiac and
renal complications during vasopressin infusions. (171)

The exact site of action of vasopressin on the gastro-
intestinal vasculature is probably at the arteriolar level.
Peter injected india ink into the gastric and superior mesen-
teric arteries of dogs receiving vasopressin and found de-
creased capillary filling, implying that the constrictive
effect is probably just proximal to the capillaries in small
arterioles. (142) Texter, using pressure transducors connect-
ed to various segments of the superior mesenteric artery
found the greatest increase of vascular resistance and pressure
during intra-arterial infusions of vasopressin to be local-
ized to the small vessel segments of the superior mesenteric

artery. He found that vasopressin had no constrictive effect on the superior mesenteric vein and its branches. (178) Peskin injected small glass beads into the superior mesenteric artery and collected them in the portal vein to evaluate arterio-venous anastomoses in the small bowel. He noted a significant decrease in the number of beads retrieved during the intravenous infusion of vasopressin and concluded that the arterio-venous shunts were closing down in response to the vasopressin. (141) Actually, however, Peskin's results would also be consistent with arteriolar constriction proximal to the arterio-venous anastomoses. Delaney injected 20 micron-radioactive spheres into the superior mesenteric artery and recovered only 3% in the portal vein and liver. He assumed that this represented the amount of blood flowing through arterio-venous channels in the small bowel. Intravenous pitressin did not alter the percent of flow through the arterio-venous channels and he concluded that they were not the primary site of vasopressin's action. (49) Altura directly observed muscular metarterioles (arterio-venous anastomoses) in the mesentary of a rat during topical vasopressin administration by using an image splitting television microscope recording system. He noted that the metarterioles did constrict when exposed to vasopressin, but the response was two to ten times less sensitive than the response of mesenteric arterioles

to topical vasopressin. (1)   Thus, it seems that the main

constrictive effect of vasopressin is on the arterioles.

We must also remember, however, that vasopressin causes

contraction of the muscular layers of the gastro-intestinal

tract and that the flow of blood in vessels passing through

this muscular layer will be markedly decreased during the

muscular contractions. (3;63)   Although of secondary impor-

tance to the arteriolar constriction, this latter effect also

will reduce gastro-intestinal blood flow.

On a more cellular level, however, the mechanism of

vasopressin is still a mystery. Adrenalectomized dogs and

dogs with sympathectomies from L-2 caudally still respond

to vasopressin with a decrease in blood flow as monitored

in the femoral artery. (71)   Both Corliss and Ericsson have

noted that vasopressin's effects in pharmacologic doses

are antagonized by neither adrenergic blocking agents nor

vascular denervation. (46;62)   However, Gardiner found that

in dogs with circulatorily isolated carotid sinuses, sever-

ed vagi and complete lack of recordable splanchnic sympathetic

tone there was no pressor response to physiologic levels of

vasopressin (0.01 unit/kg.).   In those animals with severed

vagi but with good sympathetic tone there was an increased

sensitivity to vasopressin. (70)   This latter work suggests

that at least at physiologic levels vasopressin does depend

on an intact sympathetic system in order to exert its pressor

effect. Lewis and Reit found that pharmacologic doses of
vasopressin (2 units/kg.) in cats were able to stimulate
neither the superior cervical ganglion nor the adrenal
medulla as monitored by movement of normal and denervated
nictitating membranes respectively. (113) Hertting and
Suko found that pharmacologic doses of vasopressin were
unable to release H^3 labelled noradrenaline from sympath-
etic nerve endings in the isolated cat spleen. (91) Finally,
it has been shown that vasopressin does not change the acti-
vity of post ganglionic sympathetic nerves of the celiac
ganglion but that phenoxybenzamine and/or phentolamine will
inhibit the pressor response of physiologic doses of vaso-
pressin. (180) Thus, it seems that vasopressin's effect
is not mediated through the sympathetic nervous system;
however, it does seem that at least at physiologic doses
the catecholamines themselves help to potentiate vaso-
pressin's pressor effect. This is supported by the find-
ing that non-pressor doses of vasopressin will potentiate
the pressor effect of catecholamines. (7) This may all
be mediated through the 3'5' cyclic AMP system which was
shown by Orloff in 1962, to be involved with vasopressin's
effect on water movement through the toad bladder. (76)
Cyclic AMP is found in vascular tissue and it is known that
catecholamines increase the level of cyclic AMP in many
tissues. Possibly vasopressin and the catecholamines po-

tentiate each other's effects by increasing the availability of cyclic AMP.

There has been very little work concerning the interrelationship between vasopressin and electrolytes, (76) although it has been shown that magnesium sulfate will inhibit vasopressin induced constriction of the superior mesenteric artery. (112)

The half life of vasopressin in man is approximately fifteen minutes, being removed from the plasma and inactivated mainly during passage through the liver and kidneys. (76) The initial passage of a pharmacologic dose of vasopressin through the liver is not sufficient to modify its pressor effects. (183) The mean half life of vasopressin in the dog is 5.4 minutes and over a broad range this does not seem to vary with the concentration of vasopressin given, implying that the mechanism involved with vasopressin removal is not readily saturated.(108; 167) In rats a total of 50% of an injected dose of vasopressin is cleared by the kidneys, but only 6-7% of the dose of vasopressin can be found in the urine, implying that approximately 90% of the vasopressin taken up by the kidneys is inactivated in the kidneys. The liver accounts for clearance of another 40% of the vasopressin given while the last 10% of vasopressin is cleared by other organs in the body.(75) Vasopressin is transported by the blood where it is confined to the plasma and is relatively free from any inactivation except in pregnant females who do have a vasopressinase which can inactivate the vasopressin in plasma to a minor

extent. (107)

Clark, in 1928, first noted that repeated injections of vasopressin had progressively diminishing pressor effects. (36) Razzak noted a similar tachyphylactic response; whereas an initial bolus of 3-5 units of vasopressin in dogs caused a 50% decrease in portal venous pressure the third bolus of vasopressin at twice the dosage caused only a 25% decrease in pressure. (149) Patil, however, suggested that we are not seeing true tachyphylaxis with vasopressin. Tachyphylaxis means a decreased response to repeated doses of a drug secondary to increased receptor saturation. Several drugs are able to offset the tachyphylactic effect of vasopressin: oubain does this by increasing cardiac output, ephedrine does it by inhibiting coronary vasoconstriction and reserpine does it by blocking reflexes. Methoxamine, which has no cardiotonic effects is unable to offset the tachyphylactic effect of vasopressin. Thus, Patil is suggesting that we are dealing with a "pseudo tachyphylaxis" due to cardiac fatigue rather than receptor saturation.(138) While the question is still not settled, Nusbaum noted no tachyphylaxis in patients receiving repeated doses of 0.1-0.2 units/minute of vasopressin for gastro-intestinal bleeds. (132)

Finally, I would like to discuss some of the complications of vasopressin therapy. It should be noted again

that all of the above mentioned effects of vasopressin are
seen at pharmacologic doses; only the anti-diuretic effect
is seen at physiologic levels. The complications and side
effects of vasopressin therapy are actually the many diff-
erent functions of vasopressin which were enumerated above.
These include facial pallor, nausea, eructations, flatus,
defecation and uterine cramps, all of which are readily
controlled by decreasing the vasopressin dose. (76;151;166;182)
More serious complications include mesenteric venous throm-
bosis with bowel infarction (150), EKG changes, bradycardia,
hypertension, anginal attacks, myocardial infarction and
fluid retention. (26;124;172) Finally, several authors have
warned of the potential hazard of hepatic ischemia and
necrosis secondary to vasopressin's effect on hepatic ar-
tery blood flow. (9;132;173;106) Although I have been unable
to find an actual reference in the literature of hepatic
ischemia secondary to vasopressin infusion, Nusbaum, in
answering a question in one of his most recent articles
referred to a case of liver necrosis in a patient from
Bellevue with portal hypertension who had received a vaso-
pressin infusion for several days. Nusbaum hypothesized
unrecognized occlusion of the celiac axis on the basis of
arteriosclerotic disease so that the entire infusion of
vasopressin went from the superior mesenteric artery through
collaterals to the hepatic arterial system causing hepatic

ischemia and necrosis. (132) Baum and Nusbaum are especially
cautious about infusing vasopressin into the hepatic artery:
"If one of the branches of the hepatic artery arises from
the superior mesenteric artery the tip of the catheter must
be advanced beyond the origin of the hepatic artery in order
to prevent a decrease in arterial blood flow to the liver"
(9); "Care must be taken to avoid direct or indirect infusion
of the hepatic artery" (9); "The celiac axis is not direct-
ly infused due to the danger of hepatic necroses" (132).
It is quotations such as the above which stimulated my in-
terest in this research project, for if it could be estab-
lished that vasopressin does not represent a threat to
hepatic artery blood flow then it would follow that there
is no danger of hepatic ischemia and necrosis during celiac
infusions of vasopressin. This would be clinically signi-
ficant in that celiac catheterization is much easier and
quicker than super-selective catheterization of the left
gastric, splenic, or gastro-duodenal arteries, and in a
patient who is bleeding acutely this time factor is signi-
ficant in the overall picture of therapeutic management
and ultimate recovery.

Before discussing my specific experiment, however, it
is necessary to review what is known of the hepatic vascu-
lar system, since only with this information will we be
able to interpret my results and hypothesize about what

mechanisms might be responsible for what we are seeing.

HEPATIC VASCULAR SYSTEM

The liver is supplied by two afferent blood vessels, the hepatic artery and portal vein, which enter the liver at the hilum with the common bile duct. All three structures branch together as they penetrate the liver mass, dividing into interlobar and then interlobular branches. It is well accepted by all observers that the portal vein then gives off smaller interlobular branches which finally send branches into the lobule where they subdivide to form a network of intralobular sinusoids. These sinusoids empty into the central vein of the lobule which feeds into the sublobular veins which eventually empty into one of the hepatic veins, which are the main efferent channels of the liver. The course of the hepatic artery branches is less clear. It is known that throughout its course the hepatic artery gives off a capillary network which supplies the hepatic connective tissue and the walls of the bile ducts. From this network venules enter the portal vein so that there is some pre-sinusoidal communication between the hepatic artery and portal vein (19;34), although the capillary network between the two vessels makes it unlikely that pressure or flow differences could be transmitted from one vessel

to the other at this level. The rest (and major part) of
the arterial blood probably empties into the hepatic sinusoids
via hepatic arterioles. (45;103)

Although it is known that the portal vein supplies
most of the hepatic blood flow, there has been some disagree-
ment as to the total amount supplied by the hepatic artery.
The following figures give an idea of the general range of
hepatic artery contribution to total liver blood flow: 29.3±
3.6% (73), 26-32% (116), 30% (27;28), 12.6-24.5% (17), 14%-
50% with mean of 26% (160), 34% (164), 40% (74). The hepatic
artery blood flow, however, varies with the systemic blood
pressure. Thus, Herrick and Mann in 1938, found that the
hepatic artery contributed 10-90% of total hepatic blood
flow and Grayson found that at a systemic blood pressure
of 110 mmHg in rats the hepatic artery contributed 50% of
total blood flow, but at a systemic pressure of 80 mmHg the
hepatic artery was responsible for 80% of total hepatic
blood flow while at a systemic pressure of 130 mmHg the he-
patic artery contributed only 30% of the flow. (80) This
is probably due to autoregulation within the hepatic artery,
enabling it to decrease its resistance when perfusion pressure
is decreased thereby maintaining steady flow. The portal
vein, however, is supplied by vessels which cannot autoreg-
ulate, and therefore, when the systemic blood pressure is
lowered the mesenteric, splenic and gastric arteries are

poorly perfused and as a result the portal venous flow drops
so that the hepatic artery's relative contribution to total
hepatic blood flow is increased. Conversly, when the per-
fusion pressure of the hepatic artery is increased autoreg-
ulation maintains hepatic artery blood flow at a fairly
constant level by increasing the vascular resistance. The
key to autoregulation is that blood flow and perfusion pressure
are not a linear relationship. (23;41;88;175;176) The
mechanism of hepatic artery autoregulation is probably a
myogenic constriction in the vessel walls triggered by a
rise in hepatic artery pressure; it is not dependent on
innervation of the liver. (88) It seems that the portal
vein lacks this ability to maintain its flow by regulating
its vascular resistance in the face of portal pressure
changes, and thus, in the portal vein pressure and flow
are a linear relationship and there is no autoregulation.
(23;101;174;175) This will be discussed later in more detail
in relation to reciprocal portal vein and hepatic artery
flows.

Although the hepatic artery supplies on the average only
25% of the total liver blood flow it is responsible for
32-100% of total hepatic oxygen uptake, with a mean value
of 70%. (21;83) If the hepatic artery is constricted the
oxygen content of the hepatic vein falls to less than one
volume percent. (17) However, when the portal venous flow

is markedly reduced during vasopressin infusion the hepatic

oxygen consumption is not decreased since the hepatic artery

is able to maintain it at normal levels. (48) Also recall

that the hepatic artery is responsible for the nutrition

and oxygenation of the bile ducts and liver connective

tissue so that a loss of hepatic arterial blood flow could

be lethal secondary to necrosis of these basic liver struc-

tures. (86) This is confirmed by experimental data. If the

common hepatic artery of dogs is ligated proximal to its

hepatic branches but distal to the right gastric artery

(to eliminate most of the collateral circulation) all of

the dogs die within a few days. (40;93;147) Cameron found

similar results in the rabbit. (34) In the animals which

died the liver was necrotic and the abdomen was distended

and filled with foul smelling gas and spore forming bacilli

and lecithinase, which has been identified with the alpha

toxin of Clostridium Perfringens type A organisms, were

found throughout the abdominal cavity and within the necrotic

liver. (177) It seems that ligation of the hepatic artery

and all its branches lowers the hepatic oxygen content to

such a degree that anaerobic bacteria are able to prolif-

erate. (148) These animals also deplete their glycogen

stores and become hypoglycemic in an effort to maintain

an adequate metabolic state. (34;40) Interestingly, if

penicillin is given to these animals for ten days after

hepatic artery ligation they do well and do not die. (148;177)
Presumably, penicillin prevents the anaerobic bacterial
overgrowth and within the ten day period sufficient arterial
collateralization of the liver is established so that the
hepatic oxygen content can be maintained at a high enough
level to prevent anaerobic bacterial proliferation once the
penicillin is stopped. This is further supported by the fact
that ligation of the hepatic artery and its branches in
stages over several weeks permits collateral vessels to
contribute to the liver's oxygen content so that eventually
the animal's hepatic artery and all of its branches are
ligated yet the animal can live. (91) Analogous results
have been found with ligation of the hepatic artery in man.
(77) This is all very relevant to my research, for if vaso-
pressin does cause constriction of the hepatic artery it
would in effect be a sudden "medical" ligation of the
artery with the possible fatal results described above.

The total hepatic blood flow in most mammals is 100-
130 ml./minute/100 gram of liver. (83) This total hepatic
blood flow is fairly constant when systemic arterial blood
pressure is maintained between 60 and 160 mmHg. (79) Below
60 mmHg the total hepatic blood flow rapidly falls, and a-
bove 160 mmHg the total flow rapidly increases, but within
that range the hepatic arterial and portal venous flows are
able to interact in such a way as to keep the total flow

stable under physiologic conditions. The spleen helps to keep the hepatic flow stable by compensating for changes in mesenteric blood flow; if the spleen is removed the hepatic blood flow varies more markedly with changes in systemic blood pressure. (79) Interestingly, a PCO_2 greater than 56 also has been associated with a total hepatic blood flow that is hypersensitive to changes in systemic blood pressure. (61) It seems, however, that the liver is "over-perfused" in the sense that it is able to function normally when its total blood flow is reduced by as much as 50%. Although BSP removal falls proportionately with progressive decline in hepatic blood flow, glucose metabolism and utilization by the liver (20) and galactose uptake by the liver (94) are both unaffected by total hepatic blood flows as low as 50% of normal in man and dogs. As we saw above, however, it is necessary for the fall in total hepatic blood flow to be secondary to a fall in portal venous flow, since the hepatic artery flow is crucial for hepatic oxygenation.

The status of sphincters within the hepatic vasculature is still unclear; man most probably does not have hepatic sphincters but the situation is less certain in other mammals. (83) Bauer demonstrated thick muscular coats along the hepatic vein near its junction with the inferior vena cava in dogs and correlated this with a sphincter mechanism stimulated by histamine which prevents the outflow of blood

from the liver (8); similar conclusions were reached by
Walker (189) and Moreno (125), both using the dog as an
experimental model. Arey demonstrated circular and spiral
muscles in the tunica media of the central and small sublob-
ular veins of dog using wax model reconstructions and
questioned whether their function was one of restricting
flow or of milking the veins to keep blood moving through
the liver. (2) In thirty mammals studied only the dog,
seal and racoon had this muscular arrangement. (2) Deysach
demonstrated muscular sphincters at the level of the sub-
lobular vein and Knisely demonstrated them at the sinusoidal
level. (189) Thus, it seems that the hepatic venous system
of dogs does have at least the potential for sphincter effects
at several different places. (68) This difference between
the dog's hepatic vasculature and man's will need to be
taken into consideration when trying to apply the results
from my experiment with dogs to a clinical situation with
man.

The hepatic nerve plexus receives fibres from the celiac
plexus, the vagi, and the right phrenic nerve. (83) The
vessels are innervated by both alpha and beta adrenergic
fibres as well as parasympathetic cholinergic fibres, but
the most potent effect on the vessels is that of the alpha
adrenergic fibres. (72;83) Graded electrical stimulation
of single fibres of the hepatic plexus leads to a graded

response of vasoconstriction in the hepatic artery imply-
ing that each fibre controls the vasculature of only a small
part of the liver. (29) Stimulation of the entire hepatic
plexus lead to a marked decrease in hepatic artery flow
with an increase in hepatic artery pressure (27), but as the
stimulation is maintained the hepatic artery "escapes" via
autoregulation and within five minutes the hepatic artery
flow is back to baseline values. (83) It seems that stim-
ulation of the hepatic plexus has little effect on portal
venous flow although it does increase portal venous pressure.
(30;83) As would be expected, the in vivo isolated and
denervated liver lacks most of its vasomotor tone due to
its loss of predominantly alpha sympathetic stimulation. (24)
The hepatic artery responds as would be expected to local
infusions of epinephrine and acetylcholine with vasoconstric-
tion and vasodilatation respectively. (74) Infusion of epi-
nephrine into the portal vein increased the portal venous
pressure. (81) Finally, Wakim used quartz-rod transillu-
mination to visualize the hepatic sinusoids during hepatic
plexus stimulation in frogs and rats and noted marked con-
striction of active sinusoids within two seconds of the
onset of stimulation. (186) Thus, the hepatic plexus can
play a significant role in controlling hepatic artery blood
flow and therefore, I was careful to preserve the plexus
during surgery in order to obtain results which are as

accurate and physiologic as possible.

The gross distribution of the hepatic artery and portal vein within the liver was described above but the exact relationship between the smaller branches of these vessels and the possible existence of intrahepatic shunts are two questions which are not as easily answered. It is known that in the cirrhotic liver significant amounts of blood pass from the hepatic artery to the portal vein through dilated sinusoids. (21;153) As early as 1906, Mall injected celloidin into the hepatic artery of normal mammal livers and recovered the celloidin from the portal vein (118) implying the existence of a communication between the arterial and venous systems. Furthermore, communications between the hepato-portal systems have been visualized at the sinusoidal level using quartz-rod transillumination in the amphibian, rat and mouse. (18;188) We have already mentioned that hepatic artery branches which supply the bile ducts and connective tissue empty into the portal vein before it reaches the hepatic sinusoids. These anastomoses are less than 50 microns in diameter and are of questionable functional significance. (83) Geumei claims to have demonstrated the presence of unidirectional pre-sinusoidal shunts from the arterial to the venous system in isolated perfused dog livers. He found the sum of hepatic artery and portal vein flows during independent perfusions to be greater than

their total flow during simultaneous perfusion and claimed
that during simultaneous perfusion part of the arterial blood
travels through shunts to the portal vein and impedes the
venous flow. When he clamped the hepatic vein and perfused
through the hepatic artery the perfusate appeared so rapidly
from the portal vein that he felt the shunt had to be pre-
sinusoidal based on temporal factors. When he perfused
through the portal vein all of the perfusate appeared in
the hepatic vein and none was found in the hepatic artery,
strongly implying that the shunt is uni-directional. Fur-
thermore, when nylidrin was perfused through the hepatic
artery it effected arterial and venous flow, but when per-
fused through the portal vein it effected only venous flow,
again implying a uni-directional shunt. Finally, increasing
arterial perfusion pressure led to an increase in flow in
all three vessels, but increasing portal venous perfusion
pressure increased hepatic venous and portal venous flow
but decreased hepatic artery flow implying that less arterial
perfusate was able to pass through the arterio-venous shunts.
(72;73) When Krypton 85 is injected into the portal vein
and hepatic artery both independently and simultaneously
the flow through the hepatic artery is always 75% slower
than the flow through the portal vein and the simultaneous
washout curve has been found to have either two or three
exponential components. (16;92) This has been interpreted
as representing different channels through the hepatic sin-

usoids; the fast component represents pure portal vein channels, the medium component represents channels where venous and arterial flows are mixing, and the third, slow component, represents pure hepatic artery channels. (83) Finally, it was shown by Cohn that sinusoidal perfusion by the hepatic artery is as extensive as perfusion by the portal vein as studied in the intact dog. He perfused labelled albumin and labelled red blood cells through each vessel and found the ratio of Albumin/RBC perfusion time to be the same for each vessel. In both cases the transit time of albumin was greater than that for the red blood cells implying that the albumin distributes itself in a larger space with a lower hematocrit, such as the hepatic sinusoids. If the hepatic artery bypassed the sinusoidal space its albumin time would equal its red blood cell time. This was not the case; the ratio of albumin to RBC time for the portal vein and hepatic artery were identical within experimental error. (39) Thus, it seems that there are intra-hepatic communications between the hepatic arterioles and portal venules either at the sinusoidal or pre-sinusoidal level. This is an important point as will become apparent as we discuss reciprocal arterial-venous flows and autoregulation.

We have already discussed autoregulation within the hepatic artery. Autoregulation is also involved with reciprocal flows between the portal vein and hepatic artery.

As early as 1911, Burton-Opitz found that hepatic artery
flow in the dog increased approximately 15% when portal venous
flow was shunted away from the liver toward the renal vein.
(28) Since that time several investigators have shown that
in both the intact and the isolated liver in mammals (includ-
ing man and the dog) a decrease in portal venous flow and
pressure is followed by a significant increase in hepatic
arterial flow, while an increase in portal venous flow and
pressure is followed by a decrease in hepatic artery flow.
(23;31;39;41;83;88;99;101;103;156;160;169;175) Similar
but much less pronounced reactions are seen in the portal
venous pressure, but not flow, in response to changes of
flow and pressure in the hepatic artery. (83;169;179) This
is what is known as reciprocal flow between the hepatic artery
and portal vein. It has been found that the hepatic artery
response is less marked and slower in its onset when the
hepatic plexus is intact. (39) The phenomenon is a local
response of the hepatic vasculature and is not dependent
upon the innervation of the liver. (8;39;156) Since it
supplies only 25% or so of the total hepatic blood flow,
the hepatic artery cannot completely compensate for the de-
crease in volume of portal venous flow. (23;83) It can,
however, compensate for the loss of portal vein oxygen con-
tent, and we have already shown that the liver can function
normally at 50% of baseline portal venous flow(20;94) if

its oxygen content is maintained.

The mechanism for the reciprocal flow between portal vein and hepatic artery is not perfectly understood. In most other organs of the body autoregulation serves a metabolic function in that the accumulation of metabolic products leads to a decrease in arterial resistance so that arterial flow can increase and wash out the metabolic products. Thus, the metabolic theory of autoregulation is a flow dependent one; it implies that an increase in venous pressure would lead to decreased flow and an accumulation of metabolic products which would then cause a decrease in arterial resistance and a secondary increase in arterial flow. In the liver, however, increased hepatic venous pressure leads to an increase in hepatic artery resistance with a decrease in hepatic artery flow. (83) Therefore, the metabolic theory of autoregulation does not apply to the liver. (83) A second possible mechanism is that the decrease in portal flow leads to a decrease in volumetric encroachment by portal vein radicles on the hepatic artery and as a result the hepatic artery is able to increase its flow. (156) When one considers, however, the difference in pressures between the hepatic artery (@100mmHg) and the portal vein (@10mmHg) it becomes hard to imagine the latter exerting a volumetric encroachment on the former. (68) A third possible mechanism for the autoregulation and reciprocal flow is that

the increased arterial or venous pressure causes increased

capillary filtration with fluid accumulation in the extra-

vascular space which would increase tissue hydrostatic pressure

and extrinsically compress the hepatic blood vessels reducing

their flow. This seems unlikely as the mechanism, however,

for it would exert a qualitatively identical effect on the

arterial and venous flows, while we already know that the

flows in the two systems vary inversely with respect to each

other. Furthermore, the effect on the portal venous system

would be greater since it is thin walled, but we know that

almost all of the articles referred to above found greater

responses in the arterial system.

The fourth possible mechanism is the most likely; auto-

regulation and reciprocal flow are probably the result of

a myogenic response by the terminal hepatic arterioles to

changes in pressure. We have already established that there

are either sinusoidal or pre-sinusoidal communications

between the hepatic arterial and portal venous systems and

we know that the sinusoidal system feeds into the hepatic

venous system. Thus, the hepatic artery, portal vein and

hepatic vein can all communicate via the hepatic sinusoids.

An increase in the sinusoidal pressure either secondary to

increased hepatic vein pressure, increased portal vein pressure

or increased hepatic artery pressure could lead to an in-

crease in the rhythmic activity of the smooth muscle in the

hepatic arteriole walls causing vasoconstriction and decreased
hepatic artery flow. Since the portal vein contributes more
to sinusoidal flow than the hepatic artery it is consistent
with this theory that changes in portal venous pressure are
45 times more effective than changes in arterial pressure
in affecting hepatic arterial resistance and flow. (88)
This is also consistent with Nakata's finding that 40% of
the total pressure gradient across the liver is between the
portal venules and the central vein; ie. the hepatic sinusoids,
implying that this region is important for pressure changes.
(126) The myogenic theory of autoregulation is consistent
with the observed phenomena of arterial-venous reciprocal
flow in the liver: when pressure increases in either the
hepatic vein, portal vein or hepatic artery the pressure
in the hepatic sinusoids is also elevated which elevates
the pressure in the hepatic arteriole resistance vessels
causing a myogenic constriction in these vessels. When the
pressure is reduced in either the hepatic vein, portal vein
or hepatic artery the sinusoidal pressure would secondarily
also be decreased as would the pressure in the terminal
hepatic arterioles allowing the myogenic response to relax,
thereby decreasing the hepatic artery's resistance and
increasing its flow. (88) When the sinusoidal pressure is
suddenly lowered the hepatic artery has a brief period of
excess reactive hyperemia which lasts approximately 30 seconds.

(83) I will refer back to this myogenic mechanism of auto-
regulation when discussing the results from my experiment
since the theory is crucial in interpreting my data.

Before discussing angiography I would like to briefly
discuss the anatomy of the celiac axis and superior mesen-
teric artery, since these are the vessels with which we will
be dealing. The celiac and superior mesenteric arteries are
formed from the ventral segmental arteries of the paired
dorsal aorta which constitute the arterial part of the
omphalomesenteric arc of the embryonic circulation. These
ventral segmental arteries are highly irregular in their
manner of origin which may account for the many anatomical
variations which occur between the celiac artery and the SMA.
(115;139)

In dogs the celiac trunk is 12-15 mm long and arises
from the anterior abdominal aorta between the upper borders
of the first and second lumbar vertebrae. It then trifur-
cates into a common hepatic artery, splenic artery and left
gastric artery. In 20% of animals the left gastric artery
comes off of the common hepatic artery. (60) The common
hepatic artery is 3.5-4.1 mm in diameter and moves upwards,
forwards and to the right from the celiac axis for a total
of six centimeters to the Porta of the liver where it takes
a sharp turn forward and to the right, giving off two to
four proper hepatic arteries to the liver from its convexity

and then continues to the right, forwards and downward as the
gastroduodenal artery. The gastroduodenal artery gives off
one or two right gastro-epiploic arteries and then termin-
ates in one or two superior pancreatico-duodenal arteries.
The splenic artery is 2-3 mm in diameter and moves forward
and to the left from the celiac axis. It then arches down-
ward and forward giving off several branches to the spleen.
The left gastric artery is 2-3.5 mm in diameter and moves
upwards, forwards and slightly to the left from the celiac
axis giving off numerous branches to the upper part of the
stomach. The right gastric artery is .2-.7mm in diameter
and usually arises from the gastro-duodenal but occassion-
ally comes off of a proper hepatic artery. The above data
is from a study of celiac angiograms in 24 normal dogs. (60)
A celiac angiogram from one of my experiments is on page A-1.

In man the hepatic artery, celiac axis and superior
mesenteric arteries may be quite irregular. In his study
of 200 human cadavers Michels found that the celiac axis
and SMA conformed to textbook description in only 55% of
cases. He describes twenty six collateral pathways to the
liver.(123) In 175 selective celiac and SMA arteriograms
in man only 65% had the classical textbook distributions.
(185) The most common variations include the hepatic
artery arising from the left gastric artery or the superior
mesenteric artery;Grant found the right hepatic artery

coming off of the superior mesenteric artery in 12% of human
autopsies. Woodburne found a 14% incidence of the same
anomaly. (78;191) The celiac artery and SMA arising from
a common trunk has been found in 1.4% of 853 consecutive
autopsies. (115) These arterial anomalies increase the
clinical significance of my results, for if there is in-
deed a danger of reduced hepatic artery blood flow with
secondary hepatic ischemia during direct infusion of
vasopressin into the hepatic artery, then not only celiac
infusions, but also SMA and gastric artery infusions
would be contraindicated unless the anomalous hepatic
artery could be identified and the catheter positioned so
that the vasopressin could be infused distally to the ori-
gin of the hepatic artery. All of this requires time which
is valuable in a patient who is acutely bleeding and which
need not be wasted if it could be established that direct
intra-arterial infusion of vasopressin does not represent
a threat to hepatic artery blood flow.

ANGIOGRAPHY

The principle of infusing radio-opaque dye into vessels
to delineate vascular lesions has been employed for many
years in radiology. It was in 1963, however, that Baum and
Nusbaum first investigated the use of angiography for the

demonstration of intra-abdominal bleeding from undetermined

sites. (129) They created bleeding points in the gastro-

intestinal tract of dogs and then explored several different

techniques for localizing the bleeding site. The injection

of I^{131} and P^{32} tagged albumin was no good because the back-

ground count was too high to localize the bleeding site;

aortography via a midstream injection did not sufficiently

visualize the smaller arterial branches and involved the

use of high doses of contrast material; retrograde aortography

after occlusion of the aorta with a balloon catheter above

the celiac axis visualized the peripheral branches well but

was a fairly dangerous procedure; operative segmental arterio-

graphy was time consuming and dangerous requiring at least

ten intra-operative injections since each arcade needs to

be examined separately. (10) Percutaneous selective arterio-

graphy via the femoral artery using the Seldinger technique

of catheter insertion (163) and radio-opaque polythene

catheters shaped by immersion in hot water as described

by Odman (136) was found to be an excellent procedure.

Using this technique Baum and Nusbaum were able to visualize

lesions bleeding at a rate as slow as 0.5cc/minute; only a

minimal amount of contrast material was needed. (10;129)

Vessels as small as 0.2mm in diameter can be readily visu-

alized by this technique. (60) This technique is especially

valuable considering that in 20% of patients explored for

an upper gastro-intestinal bleed and in 70% of patients

explored for melena the surgeon cannot find a source of

bleeding; conventional radiology cannot demonstrate a source

of bleeding in 20-30% of cases. (13) Selective catheteriz-

ation is superior to gastroscopy and esophagoscopy in that

the latter procedures offer the examiner only a limited field

of vision, and it is superior to conventional radiologic

techniques in that one cannot be sure that a lesion seen on

barium enema or upper gastro-intestinal series is actively

bleeding. (11) Using selective catheterization of the celiac,

superior mesenteric, and inferipr mesenteric arteries both

individually and in combination the following bleeding sites

have been identified in patients by Baum and Nusbaum: Mallory

Weiss tears, gastric ulcer, duodenal ulcer, arterial-venous

malformations, splenic rupture, esophageal varices, pancreatic

carcinoma, hepatic carcinoma, gastric carcinoma, colonic

carcinoma, pancreatic cysts, occlusive vascular disease,

pancreatitis, arterial aneurysms, peri-cecal abscess, colonic

diverticulum, and post operative bleeding from pseudo an-

eurysms at anastamoses. (10;11;12;13;16;131;184)

I have already discussed the use of intra-arterial

infusions of vasopressin to control gastro-intestinal bleed-

ing; in retrospect this seems to be the logical next step

once the clinician has identified the bleeding site via

selective angiography. The same catheter that had been

used during angiography is used for the infusion of vaso-
pressin; the drug flows into the vessels just as the contrast
material did and therefore, any bleeding site visualized
during angiography will be exposed to vasopressin during the
drug infusion. It has also been hypothesized that small
blood clots from the tip of the catheter may help to occlude
the bleeding site. (171)

Percutaneous selective angiography does entail certain
risks. In a survey of 11,402 procedures from 204 hospitals
in the United States there were seven fatalities (0.06%),
81 serious complications (0.7%) and 325 minor complications
(3.0%). (105) The fatalities were secondary to: thrombosis
of the aorta, renal arteries or carotids; passage of the
catheter through an aortic coarctation; intramural injection
with aortic rupture; and pulmonary infarct secondary to
thrombosis of an inadvertantly punctured saphenous vein.
The serious complications included: arterial thrombosis
either at the site of puncture or further along the path
of the catheter; broken catheter tip or guide wire embolus;
arterial embolization secondary to dislodged atheromatous
material or due to intimal damage with thrombus formation
and later embolization; perforation of major vessels with
large retroperitoneal hematomas; and bowel ileus and
necrosis. Temporary arterial spasms, asymptomatic local
hematomas, asymptomatic intramural or subintimal injections,

and perforation of major vessels without late sequelae were considered minor complications. (105) Luke reported five major complications during 372 procedures, including severe arterial embolization necessitating supracondylar amputation, dissecting aneurysm, total obstruction of both popliteal arteries by atherosclerotic debris and emboli, post angiography claudication at 100 feet, an orange-sized hematoma at the puncture site, and a myocardial infarction in a patient with a previously normal EKG. (114) Haut reported a complication rate of 1.8% in 1000 procedures, mainly due to post catheterization vascular thrombosis. (89) Formanek noted thrombus formation (by x-ray) in 54% of diagnostic procedures and found that the thrombus formation was directly proportional to the duration of the catheterization and not related to the diameter of the catheter. The thrombi form rapidly, being seen in catheterizations as short as fifteen minutes; the thrombus forms as a sleeve around the catheter and is peeled from the catheter and left in place in the artery as the catheter is withdrawn. (65) Other complications of selective arteriography include catheter migration, bowel infarction, cerebral vascular accidents, spinal cord paralysis, gall bladder infarction and renal damage. (55) Melnick noted that mechanical injection of contrast material caused a brisk and forceful extension of the distal catheter with a forceful return after the injection. The force

of this "whip" was proportional to the injection pressure;
intimal lacerations and sub-intimal hematomas were found
in dogs at the point of the catheter's whipping impact. (121)
Thus, selective arteriography is a useful technique, but
like all medical procedures it does entail certain risks.

PERTINENT PREVIOUS WORK

Having provided the groundwork of information required
to intelligently evaluate and interpret my data, I would
now like to briefly discuss those experiments which were
concerned with a question similar to the one with which I
have dealt; ie., the effect of vasopressin on hepatic artery
blood flow.

Heimburger infused vasopressin intravenously into dogs
and noted a 72% decrease in portal venous blood flow, a 26%
decrease in portal venous pressure and a 34% decrease in he-
patic vein flow. The changes in portal pressure and flow
persisted for fifteen to twenty minutes after the vaso-
pressin infusion was stopped, but the initial decrease in
total hepatic venous flow was followed by a gradual rise in
flow almost returning to pre-infusion baseline values while
the infusion of vasopressin was still in progress. Since
the fall in hepatic venous flow was less than the fall in
portal venous flow Heimburger postulated that the hepatic

artery blood flow had increased during the vasopressin infusion to make up for the difference between the venous flows. (90)

In 1956, Kehne infused vasopressin intravenously into dogs and noted a 33% decrease in portal venous pressure. Kehne did not discuss the hepatic artery, but in two graphs in the article he showed an increase in hepatic artery pressure of approximately 140% of baseline value, which would imply a fall in hepatic artery flow during vasopressin infusion. (98)

Shoemaker injected vasopressin into the portal vein of dogs and noted a fall in portal venous pressure and flow, a rise in systemic arterial blood pressure and a slight increase in hepatic artery resistance. Since the increase in systemic blood pressure was much greater than the increase in hepatic artery resistance he hypothesized that there would be an increase in hepatic artery blood flow during vasopressin infusions. (169)

Drapanas infused vasopressin (10 units over 15 minutes) into the external jugular vein of dogs and monitored hepatic artery, SMA, and portal vein blood flows with electromagnetic flow probes. The blood flow in each of the vessels fell during vasopressin infusion. The fall in hepatic artery blood flow was not as great as the fall in portal vein blood flow, but "a significant (and sustained) reduction in arterial

inflow to the liver was noted in all experiments" during vasopressin infusion. (53)

Hanson infused vasopressin intravenously in dogs and monitored blood flows with electromagnetic flow probes. He noted a 60% decrease in portal venous flow, a 35% initial decrease in total hepatic blood flow which then increased toward baseline values during the infusion (analogous to Heimburger's observations), a 60% decrease in SMA flow and an initial fall in hepatic artery blood flow which was transient, and was followed by an increase in hepatic artery blood flow so that at ten minutes into the infusion hepatic artery blood flow was 130% of pre-infusion baseline flow. This increase in hepatic artery blood flow persisted throughout the remainder of the vasopressin infusion. (87)

Shaldon infused vasopressin intravenously in patients with and without porta-caval shunts and noted a 39% decrease in portal venous pressure, a 40% decrease in total hepatic blood flow, an 87% increase in splanchnic resistance and a 77% increase in hepatic arteriolar resistance (as calculated from wedged hepatic vein pressure). The increase in hepatic arteriolar resistance implies a decrease in hepatic artery blood flow. (165)

Razzak infused vasopressin intravenously in dogs over ten minutes and noted an immediate fall in portal vein

pressure and hepatic vein blood flow. The hepatic vein blood flow began to return toward baseline values less than half way through the infusion while the portal venous pressure remained low throughout the infusion. Razzak hypothesized (as did Heimburger and Hanson) that the return of hepatic venous flow toward baseline values was secondary to an increase in hepatic artery blood flow. (149)

Mahfouz perfused the anatomically isolated in situ canine liver with vasopressin through the hepatic artery and noted a 25% decrease in hepatic artery blood flow and a 20% decrease in portal venous blood flow. When he perfused through the portal vein there was no change in the hepatic artery blood flow and a 78% decrease in the portal venous blood flow. (117)

Cohen infused vasopressin intravenously into cats and monitored splenic artery, hepatic artery and SMA blood flows sequentially with electromagnetic flow probes. Vasopressin caused constriction of the splenic and superior mesenteric arteries with a decrease in their respective blood flows. However, the blood flow in the hepatic artery increased during the vasopressin infusion secondary to hepatic artery vasodilatation. (37)

Ericsson infused vasopressin intravenously in dogs and monitored blood flow with isotope labelled microspheres. He noted that vasopressin decreased blood flow in the

pancreas, duodenum, tongue, lungs, stomach and bowel but increased blood flow in the brain, eyes, kidney and hepatic artery. Even with marked decreases in the cardiac output blood flow to the hepatic artery was fairly constant and did not decrease during vasopressin infusions. (62;63)

Peter infused vasopressin intravenously and monitored blood flow with electromagnetic flow probes in dogs. He noted a 47.8% decrease in portal venous flow, a 67.8% decrease in gastric artery blood flow, a 63.4% decrease in SMA flow and "inconsistent" responses in the hepatic artery. In general he found an immediate decrease in hepatic artery blood flow during vasopressin infusion followed by a gradual rise back toward pre-infusion baseline values. In only one of five dogs did the hepatic artery blood flow actually increase above baseline value after its initial decrease in blood flow during the vasopressin infusion. (142)

Aronsen performed celiac, SMA and portal vein angiograms in dogs before and during intravenous infusions of vasopressin. He found that vasopressin caused a vasodilatation of the main branches of the splenic, gastric and superior mesenteric arteries with decreased filling and marked constriction of their peripheral branches. Only the hepatic artery responded to vasopressin with an increased filling of its main branches as well as its peripheral branches. (3)

Finally, Nylander also infused vasopressin intra-
venously in dogs, monitoring the drug's effects with pre-
and post-infusion angiograms. His results were similar to
Aronsen's: the central parts of the splenic, gastric and
superior mesenteric arteries dilated while their distal
parts, including the gastroduodenal artery, were markedly
constricted during vasopressin infusion. The central and
distal parts of the hepatic artery were all dilated during
the vasopressin infusion. Not only was the hepatic artery
dilated, but also the velocity of flow of contrast material
through it was increased, suggesting a decrease in hepatic
artery vascular resistance. (135)

From the above experiments it can be seen that there
is not 100% agreement on vasopressin's effect on the
hepatic artery. It seems that the overall effect of vaso-
pressin on the hepatic artery is one of vasodilatation,
yet several investigators in good experiments have shown
vasopressin to cause hepatic artery vasoconstriction. It
should be noted that in all of the above experiments in
intact animals the vasopressin was infused intravenously.
To the best of my knowledge no one has directly infused
vasopressin into the hepatic artery while monitoring the
hepatic artery blood flow to follow the entire sequence
of vasopressin's effect in the intact, anesthetized mammal.
This type of experiment would be useful for two reasons:

it would be a simple direct way of seeing exactly what does happen when vasopressin comes in contact with the hepatic artery, and it would be simulating exactly what happens in man during direct intra-celiac infusion of vasopressin to see whether or not the fear of hepatic ischemia secondary to decreased hepatic artery blood flow during vasopressin treatment of acute gastro-intestinal bleeding is justified.

Greenway, in an excellent review article in 1971 on the hepatic vascular bed in which he reviewed 415 references concluded that "detailed knowledge of the mechanisms of drug action on the hepatic vascular bed is almost non-existent. Few studies have been adequately controlled and little attempt has been made to differentiate direct and indirect effects." (83) My review of the literature leaves me with the same impression; hopefully my work on vasopressin's effect on the hepatic artery will help to clear up some of this confusion.

PART I

The intra-arterial infusion of

pitressin into the celiac axis of dogs

with electromagnetic flow probe moni-

toring of blood flow in the hepatic

artery, splenic artery and portal vein.

MATERIALS AND METHODS

Sixteen adult mongrel dogs of both sexes were used.
The animals were starved for at least eighteen hours prior
to surgery but otherwise there were no special pre-surgical
preparations.

The following procedures are described in the order
in which they were performed.

ANESTHESIA:

The animals were anesthetized with sodium pentobarbi-
tol (Nembutal© Abbott) at an initial dose of 25 mg/kg given
as a single intravenous injection. Those animals which
became light during the experiment were given additional
intravenous injections of 25 mg of Nembutal at a time,
titrating the frequency of Nembutal injections with the

animal's clinical response as judged by spontaneous move-
ments and whimpers and masseter muscle tone. An intravenous
line in a brachial vein was kept open with normal saline
at a rate of 50 cc per hour to allow immediate intravenous
injection of Nembutal when needed.

INTUBATION:

Endotracheal intubation was performed in all animals
and respirations were controlled by a mechanical ventilator
at a volume sufficient to maintain normal pulmonary move-
ments and a rate of sixteen breaths per minute. The mechan-
ical ventilator operated on room air; no supplemental
oxygen was given.

ELECTROCARDIOGRAM:

Electrocardiogram needle leads were inserted subcutan-
eously in all four extremities and a standard limb lead was
recorded via the 350-3200 A ECG pre-amplifier channel of
a Sanborn recorder. The electrocardiogram was monitored
throughout the experiment.

ARTERIAL PRESSURE RECORDINGS:

A femoral artery cutdown was performed distal to the right inguinal ligament and the right femoral artery was isolated and ligated distally with 1-0 silk. A polythene 160 PE catheter was then threaded into the femoral artery until its tip was in the aorta, a distance judged roughly by external approximation. The catheter was connected to a pressure transducer and the aortic pressure was recorded on the 350-3000 c carrier pre-amplifier channel of the San-born recorder. The Sanborn was calibrated so that a deflection of four large squares represented an arterial pressure of 200 mmHg. Systemic arterial blood pressure was monitored throughout the experiment; the blood pressure catheter was flushed with 1 cc of normal saline every fifteen minutes to prevent clot formation at the tip of the catheter.

SELECTIVE CELIAC AXIS CATHETERIZATION:

A femoral artery cutdown was performed distal to the left inguinal ligament and the left femoral artery was isolated and carefully separated from the surrounding tissue, ligating all small branches with 5-0 silk. The Seldinger technique of catheter replacement was employed to introduce

the celiac axis catheter into the femoral artery. (163)
The following equipment was used in this technique: a
puncture needle with a diamond head stilette; a flexible
rounded end metal leader, the distal end of which is even
more flexible than the rest of the leader; an adapter for
a syringe; and a Form a cath® radio opaque catheter with
an outside diameter of 0.045 inches. The catheter was pre-
shaped by immersion in hot water followed by rapid cooling
as described by Odman (136) so that the catheter had the
general shape of a walking cane with two bends forming the
distal curve; the first bend, approximately 6 cm. from the
tip of the catheter formed a 135° angle with the rest of
the catheter, while the second bend, 1 cm. from the tip
of the catheter was pointed approximately 170° in the
opposite direction of the main stem of the catheter.

The femoral artery was ligated with 1-0 silk distal
to the intended site of puncture. The puncture needle with
diamond head stilette in place was then introduced into the
femoral artery taking care to avoid puncture of the rear
arterial wall. The diamond head stilette was withdrawn
one centimeter once in the femoral artery while the needle
was advanced several centimeters into the arterial lumen.
A proximal 1-0 silk tie around the femoral artery was used
to control bleeding as the diamond head stilette was
withdrawn and the flexible metal leader was introduced

through the needle several inches into the femoral artery.
The needle was then withdrawn and the catheter was threaded
onto the metal leader into the femoral artery.

FLUOROSCOPY AND PORTABLE X-RAY:

Using the Siemens Siremobile 2 image intensifier fluoro-
scope the catheter was advanced to a point beyond the first
lumbar vertebrae and was then slowly pulled distally, ro-
tating the catheter as it was pulled until it "flowed" into
one of the aortic branches. At that point 2 cc. of 60% sodium
diatrizoate (Hypaque®) were injected into the catheter to
determine if it was in the celiac axis. If properly posi-
tioned, a portable x-ray was taken with the GE portable
x-ray machine using a Buckey table to allow more careful
examination of the celiac axis. A repeat portable x-ray
was taken after the flow probes were in place to make sure
that they were on the right vessels. The celiac catheter
was then secured with 5-0 silk at its entrance into the
femoral artery and was attached to a 50 cc. glass syringe
filled with normal saline in a Harvard infusion pump and in-
fused at a rate of approximately 0.05 cc/min. to keep the
celiac catheter open and prevent clot formation at its tip
during the surgery.

ABDOMINAL SURGERY:

A midline abdominal incision was performed from
xyphoid to pubis; all bleeding vessels were tied with
5-0 silk and the abdominal cavity was not explored until
good hemostasis was obtained. The stomach and duodenum
were then retracted caudally and toward the animal's
left exposing the Porta Hepatis. The portal vein was
carefully cleared of surrounding tissue for a length of
2 cm. distal to the union of its main tributaries. The
hepatic artery was also cleared of surrounding tissue
for an area of 2 cm. approximately midway between the
celiac axis and the Porta Hepatis. Care was taken to
avoid damaging small arterial and venous branches and to
split the nerve fibres of the hepatic plexus longitudinally
so as not to disturb the physiologic neural effects of the
hepatic plexus on the hepatic artery. The splenic artery
was then identified and a 2 cm. area was cleared on one of
its two main branches just distal to their union into the
main stem of the splenic artery. The flow probes were
then placed on their respective vessels.

FLOW METERS AND PROBES:

Five non-cannulating electromagnetic flow probes were
used with internal diameters of 1.5 mm, 2 mm., 3 mm., 4 mm.
and 8 mm. In the first eleven dogs studied only one Statham
Electromagnetic flowmeter M4001 was available, but with the
final dogs studied there were three M4001 flowmeter power
units. Each probe was calibrated for at least two of the
M4001 flowmeter units; each probe had its own magnet current,
phase control and balance control which differed for each
meter used but which were easily determined by following
Statham's directions. To calibrate the flowmeter reading
with the actual flow in cc/min. passing through the flow
probe the probe was placed around a vessel segment in a
beaker of saline; an additional amount of saline was
allowed to pass through the vessel in a given period of time
and was measured. In all cases a linear relationship was
found between flowmeter reading and actual vessel flow in
cc/min. (see diagram page A-2). Each probe was re-calibrated
every two weeks. As a further check, in every experiment
after the probes were placed on their respective vessels
in the animal the vessels were occluded with umbilical tape
to make sure that zero flow corresponded with a reading of
zero on the flowmeter. The flow probes were selected so

as to have a diameter slightly smaller than their vessel's diameter. In that way good contact was maintained between the flow probe and the vessel wall.

Once the flow probes were properly positioned 2 cc. of 60% Hypaque were again infused into the celiac catheter with fluoroscopic monitoring to make sure that the catheter had not fallen out of the celiac axis during the manipulations of surgery and probe placement; the catheter was repositioned in the celiac axis when necessary. Blood flows in the respective vessels were monitored for one half hour to allow them to stabilize prior to starting the actual experiments.

VASOPRESSIN INFUSION:

In all groups vasopressin was administered in the form of aqueous Pitressin® (Parke-Davis) standardized to contain 20 pressor units/cc. One cc. of pitressin mixed with 9 cc.'s of normal saline were infused via the Harvard infusion pump into the celiac catheter in all experiments; only the rate of infusion differed in the different groups. Immediately after the completion of each infusion the celiac axis was visualized fluoroscopically with a 2 cc. injection of 60% Hypaque to make sure that the celiac catheter had stayed in place throughout the pitressin infusion.

CONTROLS:

In each dog studied 10 cc.'s of normal saline without pitressin were infused either before or after the pitressin infusion at identical infusion rates for equivalent amounts of time while blood flows and systemic blood pressure were monitored just as in the actual experiments. Thus, each animal served as its own control.

STATISTICAL ANALYSIS:

All results were expressed as percent change in flow (or pressure) from the pre-infusion baseline value. The mean and standard error of the mean were calculated for all of the data. Comparisons were made between different groups with the T-test for paired observations. A P value less than or equal to 0.05 was considered significant. All graphs were drawn to show a range of two standard errors above and below the mean.

GROUP I:

In all experiments in this group the animals received one cc. of pitressin (20 pressor units) mixed with nine cc.'s

of normal saline infused into the celiac axis at a rate of
1 cc/min. over 10 minutes (ie., 2 pressor units/minute).

SUBGROUP I A:

This subgroup consisted of two dogs. Blood flow in
the hepatic artery of each dog was monitored continuously.
Systemic blood pressure was also monitored continuously.
Portal vein and splenic artery flows were not monitored.

SUBGROUP I B:

This subgroup consisted of only one dog. Flow in the
portal vein was monitored continuously as was systemic
blood pressure. Hepatic artery and splenic artery blood
flows were not monitored.

SUBGROUP I C:

This subgroup consisted of eight dogs in which fifteen
separate vasopressin infusions were performed. There was
a sufficient number of flow probes for the three vessels,
but only one flowmeter was available. Therefore, flows
in the three vessels were measured sequentially by switching
the different probes into the meter in succession and
resetting the meter for the given probe. With practice
it was possible to do this quickly and accurately so that
every 30 seconds the flow in another vessel could be
recorded; eg. first a value was obtained for hepatic artery
blood flow, then the portal vein probe was hooked into the
meter and a value obtained for its flow, then the splenic

artery was connected to the meter to determine its flow
and then the hepatic artery was hooked in again and so on.
The probes were always on their respective vessels, it was
simply a matter of inserting the wires from each probe into
the flowmeter in sequence.

GROUP II:

These experiments were performed several weeks after
the experiments in group I. At this time there was a suffi-
cient number of flowmeters as well as flow probes, so that
the flows in the three vessels could be monitored continu-
ously and simultaneously in all the experiments in group II.

SUBGROUP II A:

This subgroup consisted of five dogs (the same dogs
as subgroup II B) with a total of six pitressin infusions.
One cc. of pitressin (20 pressor units) mixed with nine
cc.'s of normal saline were infused into the celiac axis
at a rate of 1 cc/min. (2 pressor units/min.) over 10 minutes
in each dog.

SUBGROUP II B:

This subgroup consisted of five dogs with a total of
five pitressin infusions. One cc. of pitressin (20 pressor
units) mixed with nine cc.'s of normal saline were infused
into the celiac axis at a rate of 0.1 cc/min. (.2 pressor

unit/min.) over 60 minutes.

For a graphic summary of Part I experiments see chart #1
on page A-3.

PART II

The vascular response of the hepatic
artery to vasopressin as studied by celiac
angiography in man.

MATERIALS AND METHODS

Materials consisted of celiac axis arteriograms taken
before and during celiac axis infusion of pitressin and a
compass and a ruler for making measurements.

The celiac angiograms of 10 patients from the West
Haven Veterans' Administration Hospital who underwent
vasopressin infusion to control gastro-intestinal bleeding
were examined. Vessel diameters of equivalent branches of
the hepatic artery were measured before and after vasopressin
infusion. It was attempted to compare the same branch of
a vessel at a given distance from a constant anatomical
marker in the pre- and post-vasopressin films. The same was
done in each case for either the gastroduodenal, splenic,
or gastric arteries to serve as a comparison with the hepatic
artery changes. The hepatic artery main stem was measured
1 cm. distal to the origin of the gastroduodenal artery.
The second order hepatic branches were measured 1 cm. distal
to the first branching of the hepatic main stem. The third

order hepatic branch diameters were measured 1 cm. distal

to the branching of the second order vessels. The fourth

order vessels were measured 1 cm. distal to the branching

of the third order vessels and the fifth order hepatic

branches were measured as accurately as possible at a fixed

distance distal to the fourth order branching. The gastric

and splenic artery branches were measured in an analogous

manner to the hepatic artery. The gastroduodenal artery,

however, with only a few true branches, was analyzed by

comparing diameter changes at a given distance from its ori-

gin from the hepatic artery. See the diagram on page A-26.

RESULTS

PART I:

In both groups I and II the baseline hepatic artery blood flow ranged from 27 cc/min. to 220 cc/min. with a mean value of 79.9 cc/min.; the baseline portal vein blood flow ranged from 62 cc/min. to 355 cc/min. with a mean value of 190.2 cc/min.; the baseline splenic artery blood flow ranged from 13 cc/min. to 184 cc/min. with a mean value of 64.4 cc/min. and the baseline systemic arterial blood pressure ranged from 50 mmHg to 157 mmHg with a mean value of 109.6 mmHg. Based on these figures the hepatic artery contributed 30% of the total hepatic blood flow while the portal vein contributed 70%.

GROUP I, SUBGROUP A:

In both dogs the hepatic artery blood flow began to rapidly fall after one minute of infusion (which is how long it takes the vasopressin to pass through the catheter when infused at a rate of 1 cc/min.) from a mean baseline value of 44 cc/min. to a mean low value of 13 cc/min. at three minutes of infusion. The hepatic blood flow then steadily increased reaching a mean maximum flow of 83 cc/min. three minutes after the infusion was finished. This maximum flow persisted for nine minutes and then gradually returned

to baseline value over thirty minutes. The two control experiments showed no change in hepatic artery flow greater than 5 cc/min. in either direction. (See graph #1, page A-4: "Mean hepatic artery blood flow monitored continuously in two dogs during a total of two pitressin infusions at a dose of 2 PU/min. for 10 minutes.")

GROUP I, SUBGROUP B:

In this dog the portal vein blood flow began to rapidly fall two minutes after the pitressin infusion was started from a baseline value of 140 cc/min. to a low value of 70 cc/min. at six minutes of infusion. The portal flow remained at this low level for six minutes (ie., until 2 minutes after the end of the infusion) and then the portal flow progressively increased, reaching a value of 136 cc/min. 40 minutes after the infusion was finished. There was no significant change in flow during the saline infusion. (See graph #2, page A-5: "Portal vein flow continuously monitored in one dog during pitressin infusion at a dose of 2 PU/min. for 10 minutes.")

GROUP I, SUBGROUP C:

In this subgroup absolute flow values were converted to percent change from baseline flow. Data from subgroups A and B of group I were included in the analysis of subgroup C's data.

The hepatic artery was studied in 10 dogs a total of 17 times during pitressin infusion and 12 times during saline infusion. After one minute of pitressin infusion the mean hepatic artery blood flow suddenly fell to 68% of baseline flow (P=0.00000050; standard error=0.040) reaching a low value of 56% of baseline flow during the third minute of infusion (P=0.00000355; standard error=0.066). The mean hepatic artery blood flow then progressively increased, reaching a mean value of 130% of baseline flow during the eighth minute of infusion (P=0.035; standard error=0.118) and 141% (P=0.0046; standard error=0.083) of baseline flow during the second minute after the infusion was over. The hepatic artery blood flow then gradually returned to base-line value over the next twenty minutes. The saline control infusions did not show a significant change in blood flow. (See graph #3, page A6 :"Mean hepatic artery blood flow monitored sequentially during 17 pitressin infusions at a dose of 2 PU/min. for 10 minutes.")

The portal vein was studied in 9 dogs a total of 16 times during pitressin infusion and 11 times during saline infusion. After 1½ minutes of pitressin infusion the por-tal blood flow began to fall reaching a mean flow of 54% of baseline flow (P=0.00000239; standard error=0.052) during the sixth minute of infusion. Mean portal vein flow remain-ed in this low range until three minutes after the infusion

was over at which time portal vein flow gradually increased being at 93% of baseline value (P=0.076, standard error= 0.093) thirty minutes after the infusion was stopped. Mean portal vein flow did not vary more than 7% from baseline value during the saline control infusion. (See graph #4, page A-7: "Portal vein flow monitored sequentially during 16 pitressin infusions at 2 PU/min. for 10 minutes.")

The splenic artery was studied in 8 dogs a total of 15 times during pitressin infusion and 10 times during saline control infusion. After one minute of pitressin infusion (at the same time that hepatic artery flow decreased) the splenic blood flow began to fall reaching a mean flow of 54% of baseline flow (P=0.00000040; standard error=0.055) during the sixth minute of infusion. The splenic flow remained at approximately this low level until the infusion was over, at which time the splenic flow progressively increased being at 92% of baseline flow (P=0.0029; standard error=0.040) fifteen minutes after the infusion was finished. Splenic artery flow did not vary more than 2% from baseline during the saline control infusion. (See graph #5, page A-8: "Mean splenic artery blood flow monitored sequentially during 15 pitressin infusions at a dose of 2 PU/min. for 10 minutes.")

The mean systemic arterial blood pressure was studied in 11 dogs a total of 18 times during pitressin infusion and 13 times during saline control infusions. The blood

pressure began to increase 1½ minutes after the pitressin infusion was started (at the same time that portal vein blood flow decreased) and reached a maximum value of 136% (P=0.00000018; standard error=0.046) of baseline pressure during the eighth minute of infusion. The blood pressure remained at this level until two minutes after the infusion was stopped at which time the blood pressure fell, reaching baseline value 15 minutes after the infusion was over. Mean systemic blood pressure did not vary more than 4% during the saline control infusion. (See graph #6, page A-9 :"Mean systemic arterial blood pressure monitored continuously during 18 pitressin infusions at a dose of 2 PU/min. for 10 minutes.)

In analyzing the sequence of events in Group I it seems that the hepatic artery and splenic artery reacted immediately to pitressin with a dramatic decrease in their respective blood flows. Approximately thirty seconds later the systemic blood pressure began to increase and the portal vein blood flow began to decrease. This was followed by a progressive increase in hepatic artery blood flow until a steady state was reached of increased hepatic artery blood flow, increased systemic arterial blood pressure, decreased portal vein blood flow and decreased splenic artery blood flow. These conditions prevailed until several minutes after the infusion was stopped, at which time all values returned toward their baseline levels.

GROUP II, SUBGROUP A:

In this subgroup the hepatic artery, splenic artery, portal vein and mean systemic blood pressure were monitored simultaneously and continuously in five dogs during six infusions of pitressin (2 PU/min. for 10 min.) and five saline control infusions. Thus, the conditions were identical to those in Group I, but now three flow meters were employed so that all three flows could be observed simultaneously at any given moment, removing any element of estimation or guesswork.

One minute after the pitressin infusion was started the mean hepatic artery blood flow decreased to 74% of baseline flow (P=0.0052; standard error=0.113) and the mean splenic artery blood flow decreased to 56% of baseline flow (P=0.0068; standard error=0.117). Two minutes after the pitressin infusion was started the mean systemic arterial blood pressure began to increase and the portal vein blood flow began to decrease; at the same time the hepatic artery blood flow started to increase while the splenic artery flow continued to fall. During the eighth minute of infusion a steady state was reached: mean hepatic artery blood flow was 121% of baseline value (P=0.025; standard error=0.071), mean splenic artery blood flow was 39% of baseline value (P=0.00028; standard error=0.068) mean portal vein blood flow was 47% of baseline value (P=0.0000028; standard error=0.031) and

mean systemic blood pressure was 126% of baseline value
(P=0.0159;standard error=0.074). The hepatic artery blood
flow remained elevated for five minutes after the infusion
was finished and then gradually returned to baseline value
over the next fifteen minutes. (See graph #7, pageA-10:
"Hepatic artery blood flow monitored continuously during
6 pitressin infusions at a dose of 2 PU/min. for 10 minutes.")
The portal vein flow remained depressed until the infusion
was over and then gradually increased, being at 79% of
baseline flow thirty minutes after the infusion was over.
(See graph #8, pageA-11:"Portal vein flow monitored contin-
uously during 6 pitressin infusions at a dose of 2PU/min.
for 10 minutes.) The splenic artery blood flow remained
depressed until the infusion was over and then gradually
increased, being at 85% of baseline flow thirty minutes after
the infusion was over. (See graph #9, pageA-12: "Splenic artery
blood flow monitored continuously during 6 pitressin infusions
at a dose of 2 PU/min. for 10 minutes.) The mean systemic
blood pressure remained elevated for two minutes after the
infusion was finished and then gradually returned to base-
line level over the next ten minutes. (See graph #10, page
A-13: "Mean arterial systemic blood pressure monitored con-
tinuously during 6 pitressin infusions at a dose of 2 PU/min.
for 10 minutes.") Blood flows and pressure did not vary
significantly during the saline control infusions.

Thus, the results of Groups I C and II A were analogous, confirming that we had not introduced significant error in Group I C by evaluating the flows sequentially. To prove this statistically the hepatic artery flows during pitressin infusion from Group I C and Group II A were analyzed and graphed against each other. There was no statistically significant difference between the two experiments. (See graph #11, page A-14: "Hepatic artery flow monitored continuously during 6 pitressin infusions vs. hepatic artery flow monitored sequentially during 17 pitressin infusions.") Similar results were obtained when the portal vein flows and splenic artery flows were compared between the two experiments. (See graph #12, page A-15: "Portal vein flow monitored continuously during 6 pitressin infusions vs. portal vein flow monitored sequentially during 16 pitressin infusions." See graph #13, page A-16: "Splenic artery flow monitored continuously during 6 pitressin infusions vs. splenic artery flow monitored sequentially during 15 pitressin infusions.")

Since the results from I C and II A were equivalent and the experiments were performed under identical conditions except for monitoring the flows continuously in II A and sequentially in I C, it was decided to combine the results to analyze all of the responses to a ten minute infusion of 20 pressor units of vasopressin. One minute after the pitressin infusion was started the mean hepatic artery blood

flow decreased to 69% of baseline flow (P=0.00000024; standard error=0.041) and the mean splenic artery blood flow decreased to 79% of baseline flow (P=0.00038; standard error=0.050). At two minutes after the start of the infusion hepatic artery flow was as low as 65% of baseline flow (P= 0.00000407; standard error=0.062) but by three minutes the hepatic artery flow had already started to increase. Mean systemic arterial blood pressure began increasing 1½ minutes after the start of the pitressin infusion and portal vein blood flow began falling at the same time. The hepatic artery blood flow continued to rise until two minutes after the infusion was stopped at which time the mean hepatic artery flow was 136% of baseline flow (P=0.00011; standard error= 0.066). The hepatic flow then gradually returned to baseline over the next 15 minutes. (See graph #14, page A-17: "Hepatic artery flow during 23 pitressin infusions at a dose of 2 PU/min. for 10 minutes.") The portal vein flow went as low as 51% of baseline value (P=0.0000002; standard error= 0.040) and stayed at that level until the infusion was over at which time the portal flow began to increase, being at 89% of baseline flow 30 minutes after the infusion was over. (See graph # 15, page A-18: "Portal vein flow during 22 pitressin infusions at a dose of 2 PU/min. for 10 minutes.") The splenic artery flow fell as low as 50% of baseline flow (P=0.00000044; standard error=0.045) and stayed at that level until the in-

fusion was over, at which time the splenic artery flow increased, reaching 90% of baseline flow 30 minutes after the infusion was stopped. (See graph #16, page A-19: "Splenic artery flow during 21 pitressin infusions at a dose of 2 PU/min. for 10minutes.") The mean systemic blood pressure progressively increased after the first 1½ minutes of infusion, reaching a maximum value of 134% of baseline pressure during the eighth minute of infusion (P=0.00000003; standard error=0.040). The blood pressure remained at this level until the infusion was over at which time it returned to baseline values over twenty minutes. (See graph #17, page A-20: "Mean systemic arterial blood pressure during 24 pitressin infusions at a dose of 2 PU/min. for 10 minutes.")

The results from Groups I C, II A and their combination are analogous. The reader is refered to graph #18, page A-21 to clarify the temporal changes in flow and pressure during a ten minute intra-celiac infusion of 20 pressor units of vasopressin.

GROUP II, SUBGROUP B:

In this group the same six animals which were studied in Group II Subgroup A underwent a pitressin infusion at the rate of 0.2 Pressor Units/minute for 60 minutes while blood flows were monitored continuously. This dosage rate more closely approximates the doses used clinically.

The hepatic artery blood flow began to decrease three

minutes after the infusion was started and reached a low level of 79% of baseline flow (P=0.010; standard error=0.047) during the sixth minute of infusion. The hepatic flow then gradually increased, reaching a maximum value of 119% of baseline flow (P=0.019; standard error=0.056) during the 19th minute of infusion. It stayed at this general level of flow until the 45th minute of infusion when the hepatic artery flow decreased to 111% of baseline flow. It stayed at this level until the infusion was over at which time the hepatic flow returned to baseline values over 15 minutes. (See graph #19, pageA-22: "Hepatic artery blood flow monitored continuously during 5 pitressin infusions at a dose of 0.2 PU/min. for 60 minutes.")

The portal vein blood flow began to decrease four minutes after the infusion was started, reaching a low level of 40% of baseline flow (P=0.000010;standard error=0.052) where it approximately remained until the infusion was over, at which time the portal vein flow increased reaching a level of 81% of baseline value 100 minutes after the infusion was stopped. (See graph #20, pageA-23: "Portal vein blood flow monitored continuously during 5 pitressin infusions at a dose of 0.2 PU/min. for 60 minutes.")

The splenic artery blood flow began to fall three minutes after the infusion was started (exactly when the hepatic artery blood flow began to fall) and reached a low level

fluctuating between 32% and 21% of baseline values (P=0.000052; standard error=0.072 and P=0.00000010; standard error=0.035 respectively). The splenic artery flow remained at this level until the infusion was stopped at which time the flow began to increase, reaching 90% of baseline flow 100 minutes after the infusion was over. (See graph #21, page A-24: "Splenic artery blood flow monitored continuously during 5 pitressin infusions at a dose of 0.2 PU/min. for 60 minutes.")

The mean systemic arterial blood pressure began to increase four minutes after the infusion was started (at the same time that the portal vein flow began to fall) and reached a maximum value of 121% of baseline pressure (P=0.045; standard error=0.075) where it remained until 30 minutes into the infusion at which time the blood pressure gradually fell, reaching baseline values 10 minutes after the infusion was over. (See graph #22, page A-25: "Mean systemic arterial blood pressure monitored during 5 pitressin infusions at a dose of 0.2 PU/min. for 60 minutes.)

There was no significant change in blood flows or systemic pressure during the saline control infusions. Thus, the responses to a lower dose of pitressin infused over a prolonged period of time were qualitatively similar to the responses seen with the higher dose but shorter duration infusions; the changes in vessel flows and systemic pressure, however, were not as dramatic in the low dose infusions as

they were in the high dose infusions.

PART II:

In all ten sets of angiograms studied the hepatic artery branches (first order through fifth order) demonstrated either no change or an increase in diameter when the vasopressin infusion films were compared with the pre-infusion films.

The gastroduodenal artery showed a marked decrease in diameter throughout its length during the vasopressin infusions.

The splenic artery and gastric artery showed either no change or an increase in diameter of their main stem branches (first order) in the films taken during the vasopressin infusion. The second through fifth order branches of these arteries, however, showed either a decrease in diameter or were totally absent during the vasopressin infusions. (See chart #2, page A-27 & A-28)

Thus, intra-celiac vasopressin caused a marked constriction in the gastroduodenal artery and the peripheral branches of the splenic and gastric arteries, but had little effect upon the hepatic artery and its peripheral branches.

GENERAL DISCUSSION

In this discussion I shall be concerned with the rationale of my procedures and the implications of my results. I will not repeat theories and facts which were already discussed in the introduction; the reader will be referred back to that section when it seems appropriate.

The dog was used as my experimental model because of its large size and the similarity between its vascular anatomy and man's. It should be recalled, however, that the dog liver does have muscular hepatic sphincters which are not found in man's liver. (2;8;83;125;189) Although the function of these sphincters is not clear, it is possible that they do play a role in intra-hepatic control of liver circulation.

Although it would have been more applicable to the clinical situation in man if the animals were not anesthetized, the duration of the procedure and the abdominal surgery necessitated the use of sodium pentobarbital anesthesia. Pentobarbital (25 mg/kg) in dogs has been found to decrease cardiac output, increase hepatic artery blood flow, both increase (64) and decrease (62) splanchnic blood flow, increase heart rate, decrease mean systemic blood pressure, increase arterial PCO_2 and decrease basal body temperature. (62;64;

83;127;145) In all cases, however, the pentobarbital effect
was transitory; all values returning to normal within thirty
minutes in spite of continued anesthesia. Since I did not
begin my vasopressin infusions until approximately two hours
after the initial anesthetic dose, I feel confident in
assuming that all of the vascular parameters were stable and
that the pentobarbital did not distort my experimental results.

Since it is known that an arterial PCO_2 greater than
56 is associated with increased splanchnic vascular resistance
all of the dogs were intubated and respirations were controlled
at a normal level with a mechanical ventilator to avoid
respiratory acidosis. (61) Furthermore, since it has been
found that vasopressin has effects in the hypovolemic dog
which differ from its actions in the normovolemic animal
(62) special care was taken during surgery to achieve and
maintain good hemostasis; in addition the animals were kept
well hydrated with normal saline.

Catheterization was performed in the identical manner
as it is done in man. The Seldinger technique is a rather
clean procedure with the advantage of being able to use a
small needle for a given catheter size. (163) The Formacath
catheter was radio opaque and held its shape at body temper-
ature; the thinner tip made selective celiac catheterization
that much easier. (136) Hypaque contrast material is trans-
ported rapidly to the kidneys and excreted unchanged in the

urine; with normal renal function elimination is almost

immediate. (76) This, plus the high dilutional effect of

the small hypaque bolus in the dog's intravascular volume,

allowed one to frequently check the position of the catheter

fluoroscopically without fear of secondary effects from the

hypaque. No significant complications were encountered during

catheterization in the sixteen animals studied.

The anatomy of the celiac axis in the dogs which I

studied corresponded well with the description given by

Enge in his angiographic study of the celiac axis in dogs.

(60) In all sixteen animals the celiac axis trifurcated

into the common hepatic , left gastric, and splenic arteries;

no anomalies were noted. An attempt was made during surgery

to disturb the celiac axis and porta hepatis as little as

possible; the hepatic plexus was separated longitudinally

when cleaning the hepatic artery for probe placement so as

not to distort the physiologic neuro-vascular tone of the

vessel. No significant changes were noted in blood pressure

and heart rate either during or after surgery. Hepatic artery

spasm was noted for approximately fifteen minutes after sur-

gery and flow probe placement. Blood flows, therefore, were

allowed to stabilize for thirty minutes before pitressin in-

fusion was begun.

The three vessels studied were chosen for the following

reasons: flow changes in the hepatic artery, of course, were

my primary concern; the portal vein flow was monitored to
study the interaction of the two afferent vessels of the
liver to see if there was indeed autoregulation with recipro-
cal flow between the two vessels; the splenic artery was
monitored to serve as an arterial comparison with the hepatic
artery. The fact that both the hepatic and splenic arteries
originate from the same structure during embryonic develop-
ment (139) yet respond differently to vasopressin is quite
interesting and will be discussed later.

The electromagnetic flow probes and meters were a rather
clean and accurate way of monitoring blood flow. The electro-
lytes of blood are charged particles which move between the
magnetic poles in the flow probe and cut the magnetic lines
of force at right angles, thereby generating a voltage which
is registered by the flowmeter. Since the flow of charged
electrolytes through a blood vessel is really an "endless"
moving electrolyte solution a steady potential difference
is recorded on the flowmeter. Blood vessel walls have enough
electrical conductivity to permit placing the recording e-
lectrodes around the blood vessel without disturbing the
intravascular space. Contact between the electrodes and the
blood vessel is not essential as long as all air is excluded
from the space surrounding the vessel. The square wave
flow voltage is proportional to the number of electrolytes
(volume of blood) passing through the magnetic field; vessel

size, position and pulsation do not significantly effect the
operation of the meter when mean flow is being evaluated.
When the meter and probe are well calibrated there is a
linear relationship between flow and flow meter needle de-
flection; my calibration results were consistent with this
statement. (51;102) It is also possible to leave the flow
probes in place while the animal recovers to allow continued
monitoring of blood flow in the intact and awake animal. (146)

The effects of vasopressin were discussed in the in-
troduction. Pitressin (Parke-Davis) is an aqueous solution
of the pressor principle of the posterior pituitary gland,
substantially free from the oxytocic principle. It is stan-
dardized to contain 20 pressor units/cc. Five units sub-
cutaneously or intramuscularly three times a day are usually
adequate to give a physiologic response in Diabetes insipidus
or abdominal distention. (76) The dosages used in my ex-
periments were much greater than this; 20 pressor units intra-
arterially over 10 minutes and 12 pressor units intra-arterially
over 60 minutes.

During the 10 minute infusions the catheter position
was checked immediately after the infusion was over and
during the sixty minute infusions the catheter postion was
checked every twenty minutes; the catheter remained in place
throughout all of the infusions. All three celiac vessels
received an equal amount of hypaque before the pitressin in-

fusion was started; once the infusion was begun, however, most of the flow went to the hepatic artery. Thus, I was indeed monitoring the direct effect of vasopressin on hepatic artery blood flow.

Results were expressed as percent change from pre-infusion values, rather than as absolute values, for the purpose of statistical comparison. The absolute amount of flow in a given vessel varied significantly from animal to animal, depending on animal size, vessel size and blood pressure. The change in flow in response to vasopressin, however, was analogous in all animals in the vessels studied; this is more clearly shown by expressing the results as percent change from baseline value. Having each animal serve as its own control is an ideal way to control all variables. Conditions were identical during the pitressin and saline infusions except for the addition of pitressin in the former; any difference in results between the two groups, therefore, can be attributed to the pitressin.

I found the hepatic artery flow to be 30% of the total liver blood flow while the portal vein accounted for 70% of the flow during resting baseline measurements. This is analogous to the distribution of flow between hepatic artery and portal vein found by other investigators. (27;28;73;116; 160;164) Furthermore, in Groups I C and II A, I found hepatic artery flow to be increased 136%, portal vein flow to be

decreased 51%, and splenic artery flow to be decreased 50%
of baseline values. This corresponds well with the percent
change in flows found by other investigators during vaso-
pressin infusion. (87;90;142)

In the initial two dogs (Group I A) the hepatic artery
was studied alone. The results were dramatic and significant;
allowing pitressin one minute to travel through the celiac
catheter the hepatic artery responded to the pitressin with
an immediate fall in blood flow. This primary response,
however, was transient and was followed by a compensatory
increase in hepatic artery flow which persisted throughout
the pitressin infusion and then returned to baseline value.
The portal vein response in Group I B was also dramatic;
approximately 1½ to 2 minutes after the start of the infusion
(which is enough time for the pitressin to travel through
the catheter and circulate through the dog's vascular system)
the portal vein flow fell and remained at a low level until
the infusion was over.

It was shown that the results of Group I C with sequen-
tial monitoring of blood flow and Group II A with continuous
monitoring of blood flow were analagous with no statistically
significant difference between them. In all cases the hepatic
artery and portal vein reacted as described above. In addi-
tion, the splenic artery flow fell at the same time that the
hepatic artery flow fell, remaining at a low level throughout

the infusion. The mean systemic blood pressure increased
at the same time that the portal vein flow fell.

Thus, in all three vessels studied plus the systemic
blood pressure the responses to high doses of pitressin
(2PU/min) over a ten minute period were consistent and
dramatic. The sequence of events is as follows: Pitressin
causes a direct vasoconstriction with decreased blood flow
immediately upon arrival in the hepatic artery and splenic
artery; as the pitressin becomes systemic over the next thirty
seconds the systemic blood pressure begins to increase and the
portal venous flow falls. The hepatic artery responds to the
fall in venous flow with an increase in its own flow so that
a steady state is reached of increased hepatic artery flow
and systemic blood pressure and decreased portal vein and splenic
artery flows. This state persists throughout the infusion,
returning to baseline value once the infusion is over. The
changes in flow and blood pressure were statistically sig-
nificant with P values much lower than 0.05.

The fall in portal vein flow corresponded temporally
with the rise in systemic blood pressure, and therefore,
it was most likely due to splanchnic vasoconstriction and
decreased SMA, IMA, splenic artery and gastric artery blood
flows. This pre-portal effect of vasopressin on the portal
vein blood flow has been noted by many other observers. (4;32;36;
57;83;47;134;142;169;178) Nevertheless, I cannot rule out

at least a minor direct effect of vasopressin on the portal vein.

The initial response of the hepatic and splenic arteries (decreased blood flow) is consistent with vasopressin's effect on the rest of the splanchnic arteries. The hepatic artery, however, has a secondary response; as the portal vein flow begins to fall the hepatic artery's flow begins to rise. This is entirely consistent with the myogenic theory of reciprocal flow between the hepatic artery and portal vein which was discussed in detail in the introduction (page 33). According to this theory, as the portal venous flow decreases the pressure within the hepatic sinusoids also decreases; the terminal hepatic arterioles which communicate with the sinusoids detect this fall in sinusoidal pressure and respond with a vasodilatation of the arterial resistance vessels, increasing hepatic artery blood flow via this myogenic mechanism. The fact that the hepatic artery has the same embryologic origin as the other splanchnic arteries, yet responds differently to vasopressin, is interesting. Even more amazing is the angiographic demonstration that the gastroduodenal artery, which is actually a branch of the hepatic artery, responds to vasopressin with a prolonged vasoconstriction. This strongly implies that the autoregulatory mechanism of the hepatic artery lies in its distal branches within the liver and not in the main stem of the artery which is so

closely related ontogenetically to the other splanchnic vessels;
ie., it supports the sinusoidal-myogenic theory of hepatic
artery autoregulation.

It should be noted that the increase in hepatic artery
blood flow to 136% of baseline value will only increase total
liver blood flow 11%, while the fall in portal vein blood
flow to 51% of baseline value lowers the total liver blood
flow 36% (assuming that the hepatic artery contributes 30%
of total hepatic blood flow and the portal vein contributes
the rest). Thus, during the pitressin infusion total hepatic
blood flow is only 75% of its baseline value. We have shown
in the introduction, however, that the liver is able to func-
tion normally when portal venous flow is decreased by 50%.
(20;94) It is the oxygen content of the liver, which is
mainly provided by the hepatic artery, which is critical;
(48) the increased hepatic artery blood flow during vaso-
pressin infusion adequately maintains the liver's oxygen con-
tent and protects against ischemia.

My results do help to clarify the confusion created by
past experiments in this area. I have confirmed the indirect-
ly concluded hypothesis of Heimberger (90) Razzak(149) and
Shoemaker (169) that hepatic artery flow is increased by
vasopressin. My results are in total agreement with Hanson's
work (87) including the percent changes in vessel flows
(he found a 60% decrease in portal vein flow and a 130%

increase in hepatic artery flow as compared with my values

of 51% and 136% respectively). Cohen (37), Ericsson (62;63),

Aronsen (3), and Nylander (135) missed the primary vasocon-

striction of the hepatic artery but did note the secondary

vasodilatation during vasopressin infusion. They, like all

other investigators in this field, infused the vasopressin

intravenously. This only tends to confuse the results, since

the celiac axis, SMA and IMA all are effected by the vaso-

pressin at the same time. Thus, the portal vein flow begins

to fall at the same time that the hepatic artery flow starts

to fall, the former stimulating the myogenic autoregulatory

response in the terminal hepatic arterioles which then inhibits

the primary vasoconstrictive effect of vasopressin on the

hepatic artery. Peter's results were inconsistent (142) and

Kehne (98), Drapanas (53), Shaldon (165) and Mahfouz (117)

had results which were contradictory to mine; I am unable

to explain why this is so. The reader is referred to page

43 for a more detailed description of these experiments.

The pitressin infusions in Group II B were more analogous

to the clinical situation in the treatment of gastro-intestinal

bleeding; the pitressin dose was 0.2 PU/min. and the infusion

lasted for one hour, so that each animal received a total

dose of 12 pressor units of pitressin. The results were

qualitatively similar to the higher dose infusions of vaso-

pressin, but were much less dramatic. The fall in hepatic

artery blood flow preceded the rise in systemic blood pressure and consequent fall in portal vein flow. The hepatic artery flow then increased to 119% of its baseline value. All flow changes were statistically significant with P values less than 0.05. Thirty minutes after the infusion started, however, the systemic blood pressure gradually fell and returned to baseline level. Fifteen minutes later the hepatic artery blood flow fell to 111% of baseline level and stayed at that level until the infusion was over, at which time the hepatic artery flow returned to baseline value. Thus, there were two major differences between the high dose short duration and low dose long duration infusions: the changes in flow and pressure were more dramatic in the former, and the systemic blood pressure did not remain elevated throughout the entire infusion in the latter. Furthermore, there was a slight decrease in hepatic artery flow toward the end of the long infusion, but this was not significant and hepatic artery flow was still significantly greater than baseline flow.

In trying to explain the return of blood pressure to baseline during the long infusions one might hypothesize tiring of the vascular muscles with a consequent vasodilatation and decrease in blood pressure. However, the splenic artery and portal vein flows remained low during this period implying that the splanchnic vessels remained constricted and that if there was a vasodilatory effect it was restricted

to the peripheral arteries. It must be remembered, however, that these were long procedures taking approximately a total of six hours during which time the dog's abdomen was opened. Although the abdominal wound was covered with saline soaked towels, there was still a significant evaporative cooling effect upon the animal which may have contributed to the fall in blood pressure. This would also explain why the post-infusion flow in all three vessels was lower than the pre-infusion flow in the long infusion experiments.

The celiac angiograms from patients receiving vasopressin infusion revealed peripheral vasoconstriction of all branches of the gastric and splenic arteries in addition to constriction of the entire gastroduodenal artery while the hepatic artery and its branches were unchanged or actually slightly vasodilated. This is in agreement with the work done by Nylander in dogs (135) and further confirms the unique secondary response of the hepatic artery to vasopressin infusion. This response in man, being identical to the response of the hepatic artery in dogs, is additional support in arguing that vasopressin does not represent a threat to hepatic artery blood flow.

There are several additional experiments which might be useful to perform in this area. It has been reported (62) that hypovolemic dogs respond to vasopressin differently than normovolemic dogs. In view of the fact that many patients

who would require vasopressin infusions are hypovolemic secondary to their acute gastro-intestinal bleeds it would be
useful to bleed dogs down to a given blood pressure and then
repeat the experiments which I have performed. It would
also be useful to study the effect of intra-celiac infusions
of vasopressin in the awake dog. This could be done by placing
the flow probes on their respective vessels and then allowing the animals to recover over several weeks with the probes
in place. (146) Using animals trained to lie still, and
local anesthesia for the femoral artery cutdown, one could
then repeat the experiments which I performed under conditions
even more similar to those used with man. It would also be
interesting to repeat the experiments which I performed but
in addition take liver biopsies to confirm the absence of
hepatic necrosis. Although the latter experiment would be
interesting, it is probably not necessary in view of the
clearcut results from my experiments; hepatic necrosis would
most likely not be found.

SUMMARY

The effect of intra-celiac infusion of vasopressin on
hepatic artery blood flow was studied 28 times in 15 dogs
using non-cannulating electromagnetic flow probes. Portal
vein flow, splenic artery flow and systemic blood pressure
were also monitored. Normal saline infusions without vaso-
pressin served as controls in every animal studied.

Results were consistent in all animals. Initially,
hepatic artery flow fell to 65 percent of baseline and splenic
artery flow fell to 50 percent of baseline values. Over
the next 30 to 60 seconds systemic blood pressure began to
rise reaching a value of 134 percent of baseline and portal
vein flow fell to 51 percent of baseline. As portal vein
flow fell hepatic artery flow increased, reaching a value
of 136 percent of baseline flow. This state of increased
hepatic artery blood flow, increased systemic blood pressure,
decreased portal vein blood flow, and decreased splenic artery
blood flow persisted throughout the remainder of the vaso-
pressin infusion. All values returned to baseline post-
infusion.

Angiograms from ten patients who underwent celiac axis
infusion of vasopressin were also studied. Post vasopressin
angiograms showed no change (or an actual increase) in hepatic

artery diameters while the splenic, gastric, and gastro-duodenal arteries showed marked peripheral vasoconstriction.

On the basis of this study as well as evidence from the published studies of others, it is concluded that the hepatic artery responds to vasopressin with an initial vasoconstriction and fall in blood flow which is followed by vasodilatation and increased hepatic artery flow secondary to a myogenic autoregulatory response in the hepatic arterioles. This myogenic response is triggered by the fall in hepatic sinusoid pressure which results from the fall in portal vein blood flow secondary to pre-portal vasoconstriction caused by vasopressin. The initial fall in hepatic artery flow also helps to trigger the myogenic vasodilatation. The unique secondary increase in hepatic artery blood flow enables it to deliver more oxygen to the liver, thereby maintaining the liver's oxygen content and protecting it against ischemia and necrosis in spite of the decrease in portal vein flow.

In view of the uniform results during infusion of vasopressin in dogs, and in view of the clinical confirmation supplied by angiograms of ten patients who underwent celiac axis infusion of vasopressin, it is felt that direct celiac infusion of vasopressin does not necessarily represent a threat to hepatic artery flow. If the clinical situation

dictates, vasopressin can be infused directly into the main celiac axis without causing hepatic ischemia, provided compensatory dilatation of the hepatic artery occurs, as documented by angiography after a brief trial.

APPENDIX INDEX

Angiograms, Diagrams, Charts and Graphs

All graphs show a range of two standard errors
above and below the mean.

Selective Celiac Axis Angiogram of Dog

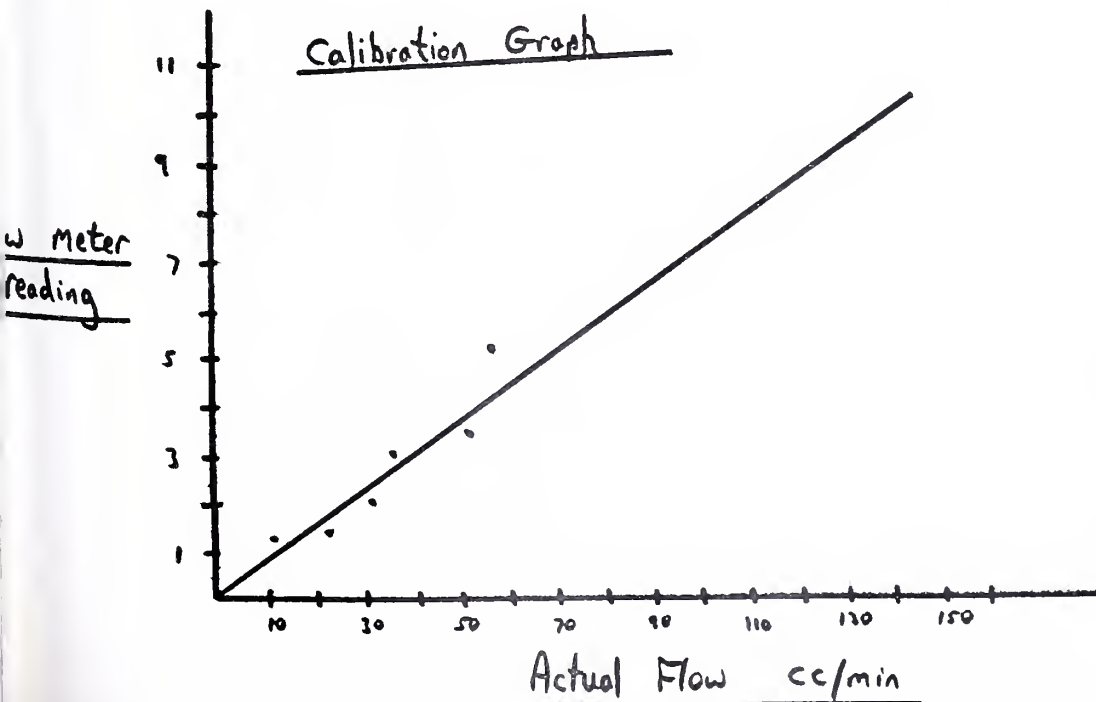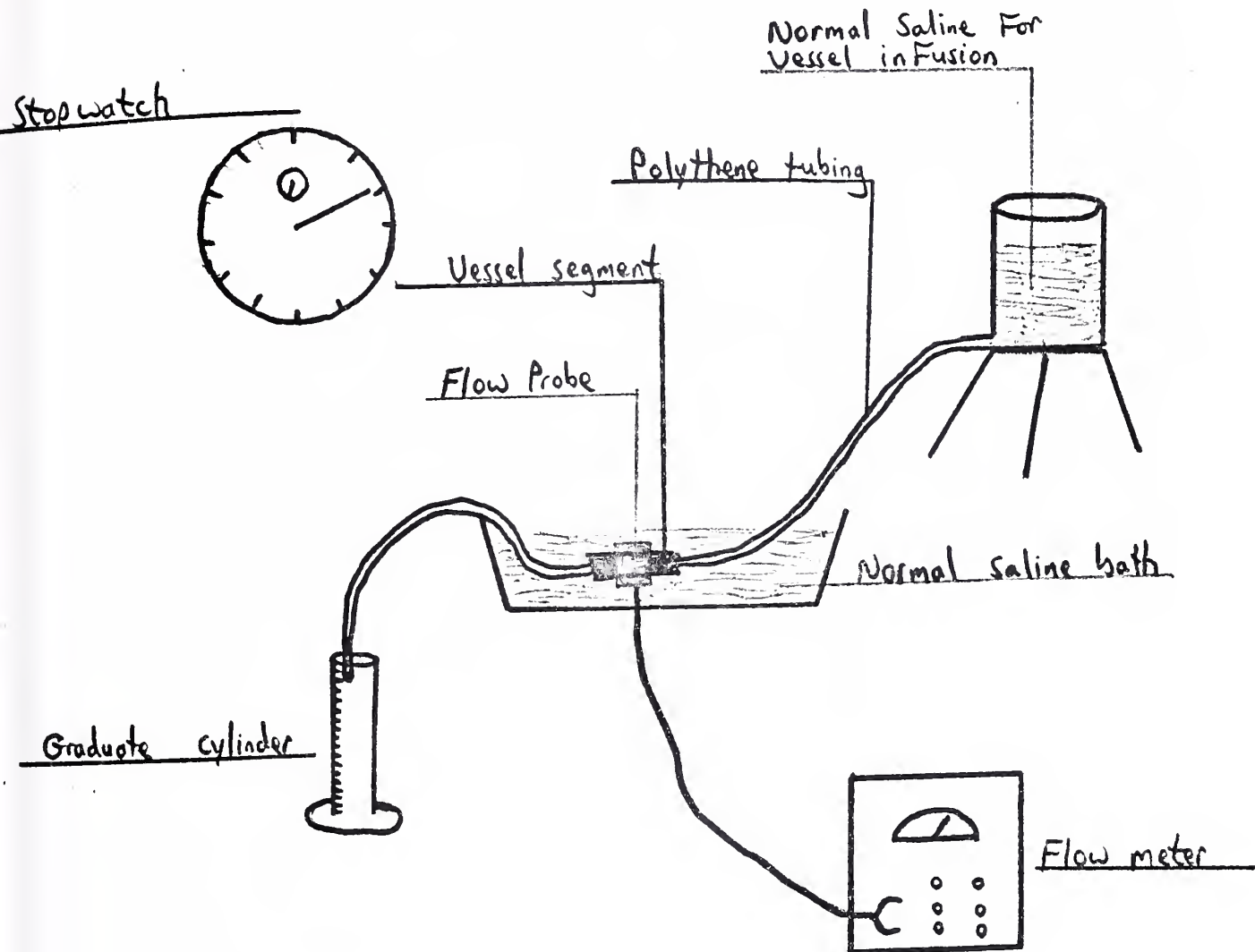A-1

Flow probe Calibration Diagram #1

Normal Saline For Vessel infusion

Polythene tubing

Stopwatch

Vessel segment

Flow Probe

Normal saline bath

Graduate cylinder

Flow meter

Calibration Graph

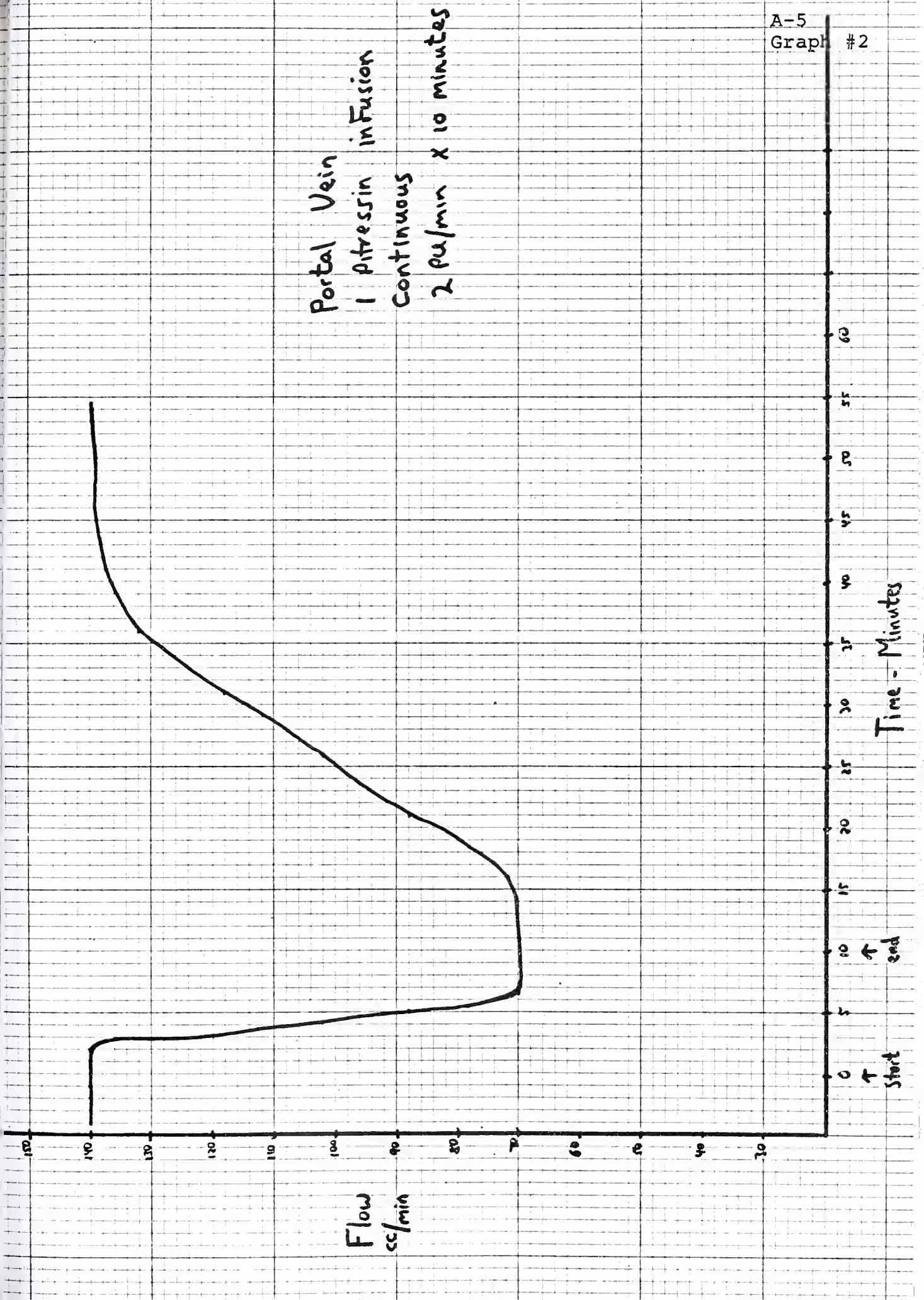Flow meter reading

Actual Flow cc/min

CHART #1

Part I: Intra-Celiac Infusion of Pitressin – Summary of Experiments

Group	Number of Dogs	Number of Pitressin Infusions	Number of Control Infusions	Pitressin Dose: Pressor Units/min. (PU/min.) X Duration of Infusion	Flow Monitored	Vessels Monitored
I A	2	2	2	2PU/min. X 10 minutes	Continuously	Hepatic Artery Systemic Blood Pressure
I B	1	1	1	2PU/min. X 10 minutes	Continuously	Portal Vein Systemic Blood Pressure
I C	8	15	10	2PU/min. X 10 minutes	Sequentially	Hepatic Artery Portal Vein Splenic Artery Systemic Blood Pressure
II A	5	6	5	2PU/min. X 10 minutes	Continuously & Sequentially	Hepatic Artery Portal Vein Splenic Artery Systemic Blood Pressure
II B	5	5	5	2PU/min. X 10 minutes	Continuously & Sequentially	Hepatic Artery Portal Vein Splenic Artery Systemic Blood Pressure

Hepatic Artery

2 Pitressin infusions.
Mean Values
Continuous

2 pu/min X 10 minutes

Flow
c.c/min

Time - Minutes

Start

end
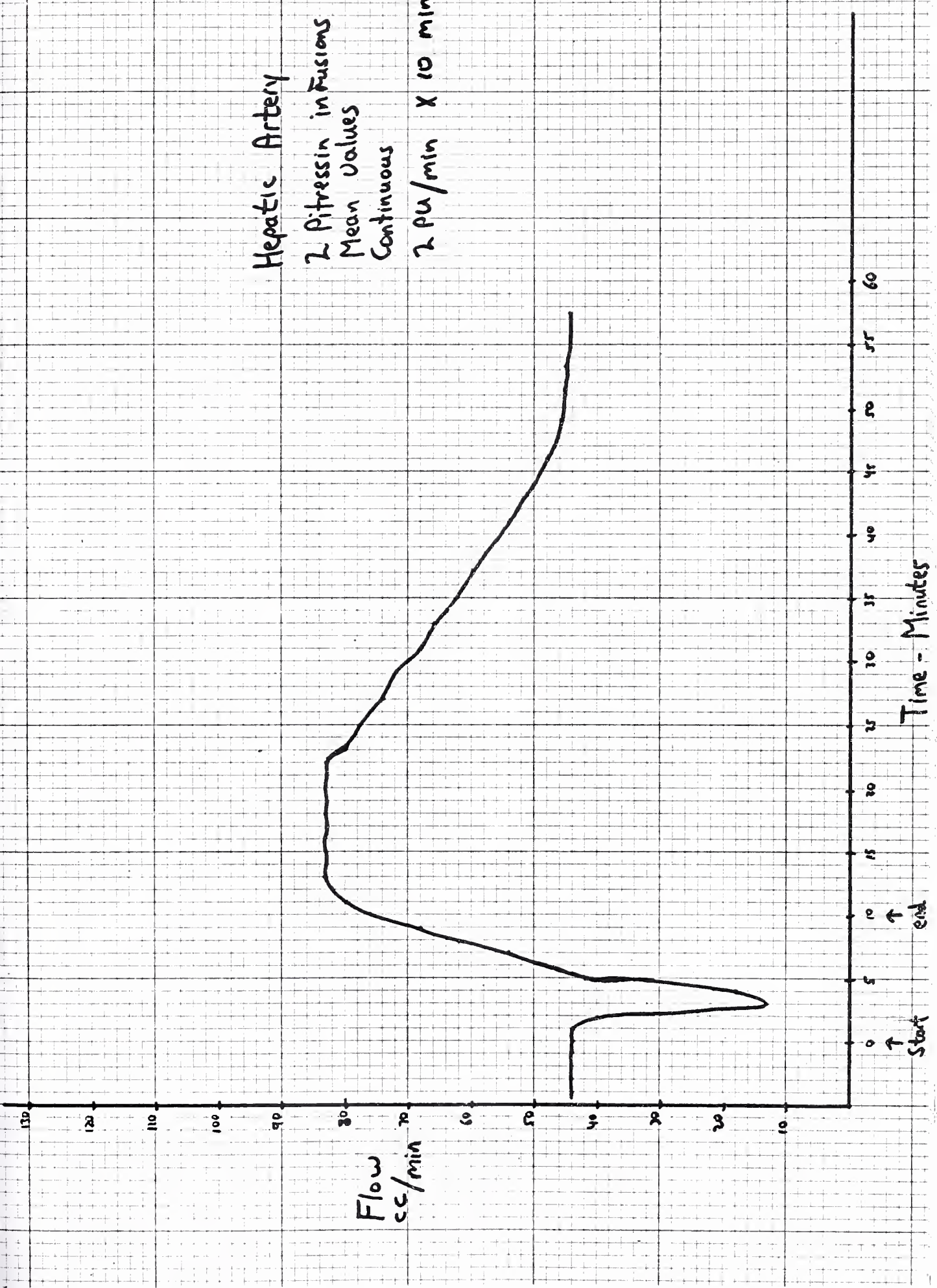
Portal Vein
1 Pitressin inFusion
Continuous
2 PU/min x 10 Minutes

Flow
cc/min

Time - Minutes

Start

End

Hepatic Artery

17 Pitressin infusions
12 Control infusions
Sequential
2 PU/min × 10 minutes

◆ = NaCl Control
— = Drug Effect

% of Baseline Flow

Time - Minutes

↑ start   ↑ end

A-7
Graph #4
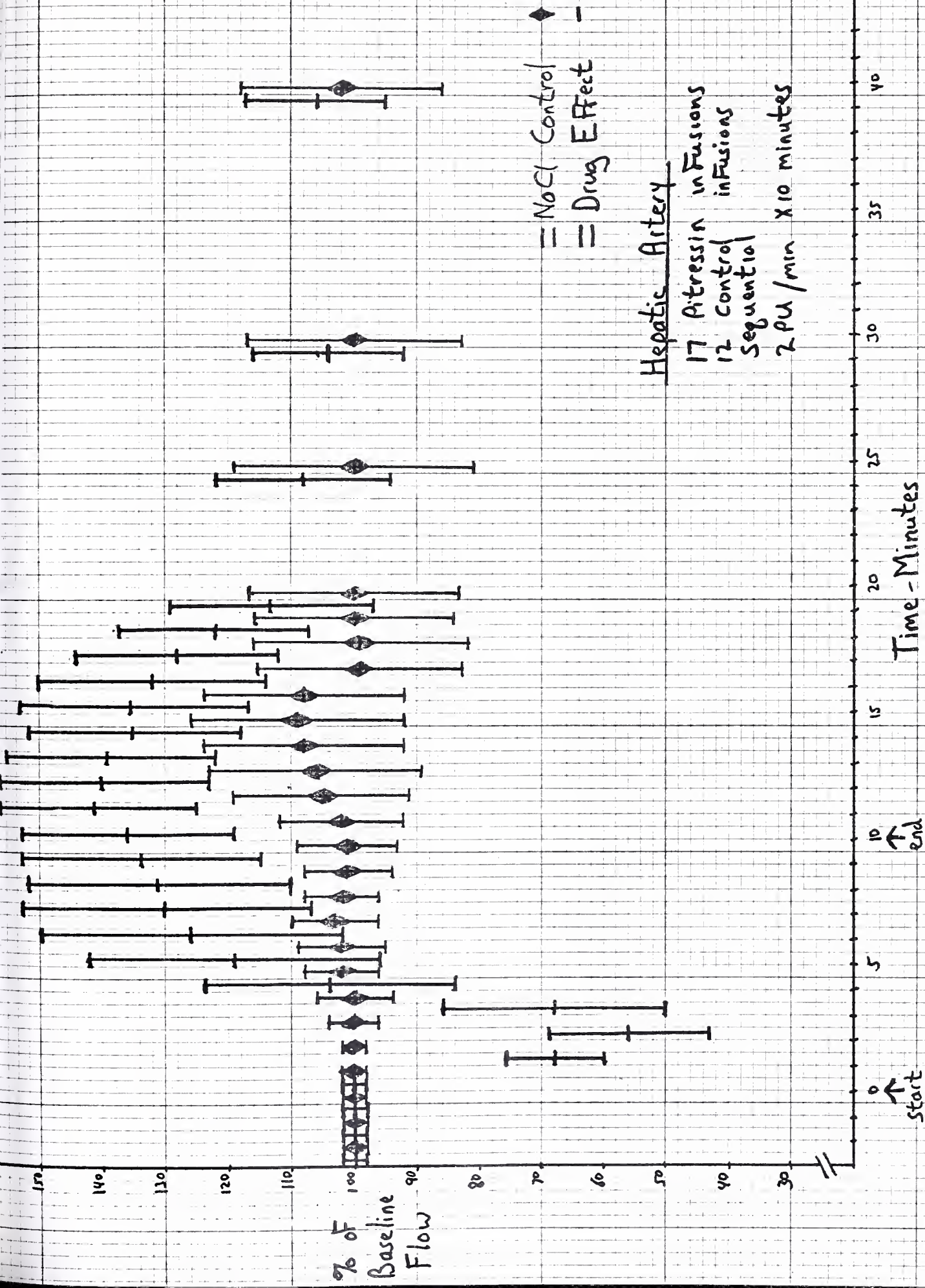
Portal Vein

16 Pitressin infusions
11 control infusions
Sequential
2 µu/min x 10 minutes

◆ = NaCl Control
■ = Drug Effect

% of Baseline Flow

Time - Minutes

Splenic Artery

= NaCl Control
= Drug Effect

15 Pitressin inFusions
10 control inFusions
sequential
2 PU/min X 10 minutes

Time - Minutes

% of Baseline Flow

Mean Systemic Arterial Blood Pressure
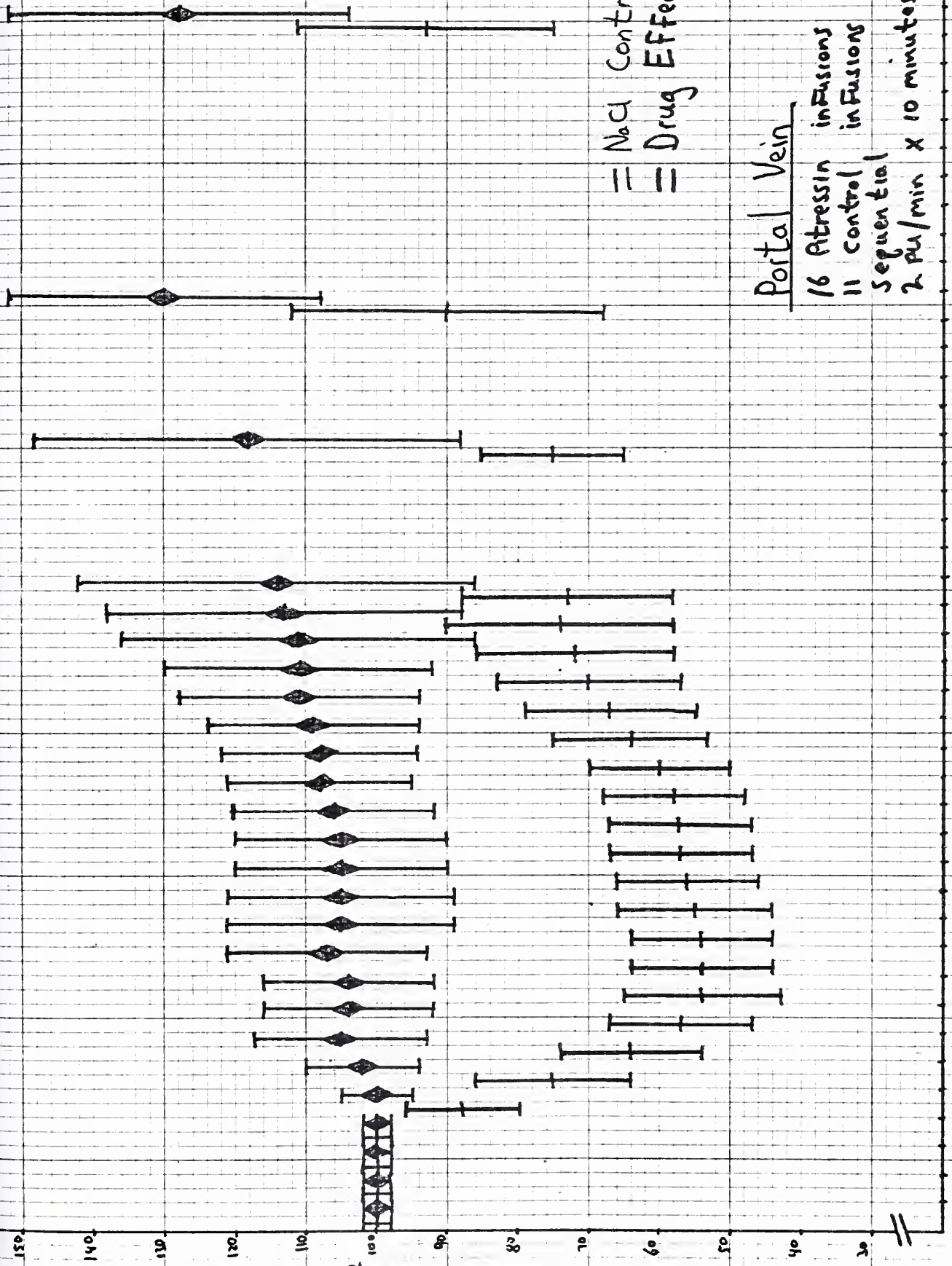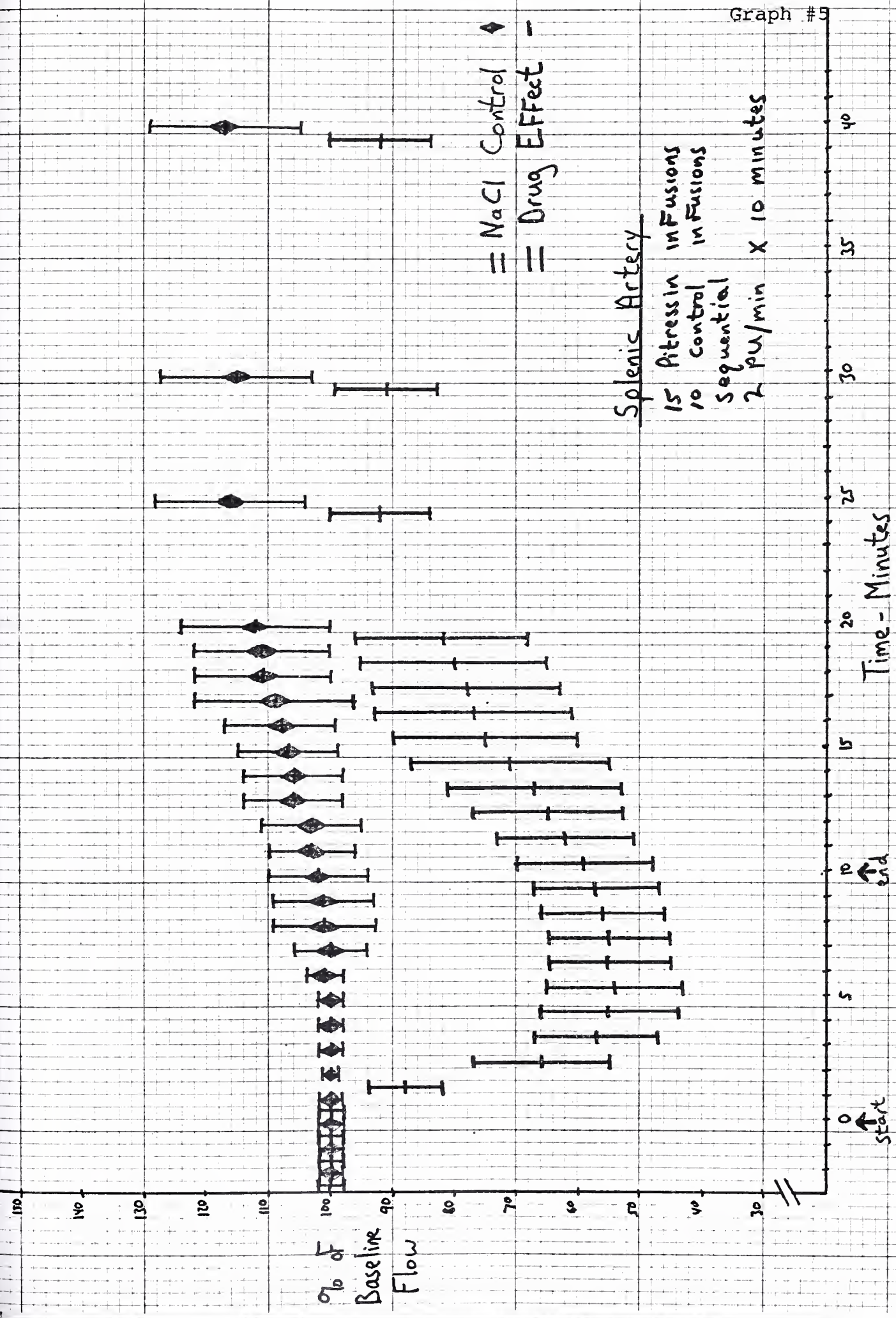
= NaCl Control ◆
= Drug Effect –

18 Pitressin   Infusions
13 control   in Fusions
continuous
2 pu/min × 10 minutes

% of
Baseline
Blood
Pressure

Time – Minutes

↑
Start

↑
end

A-10
Graph #7
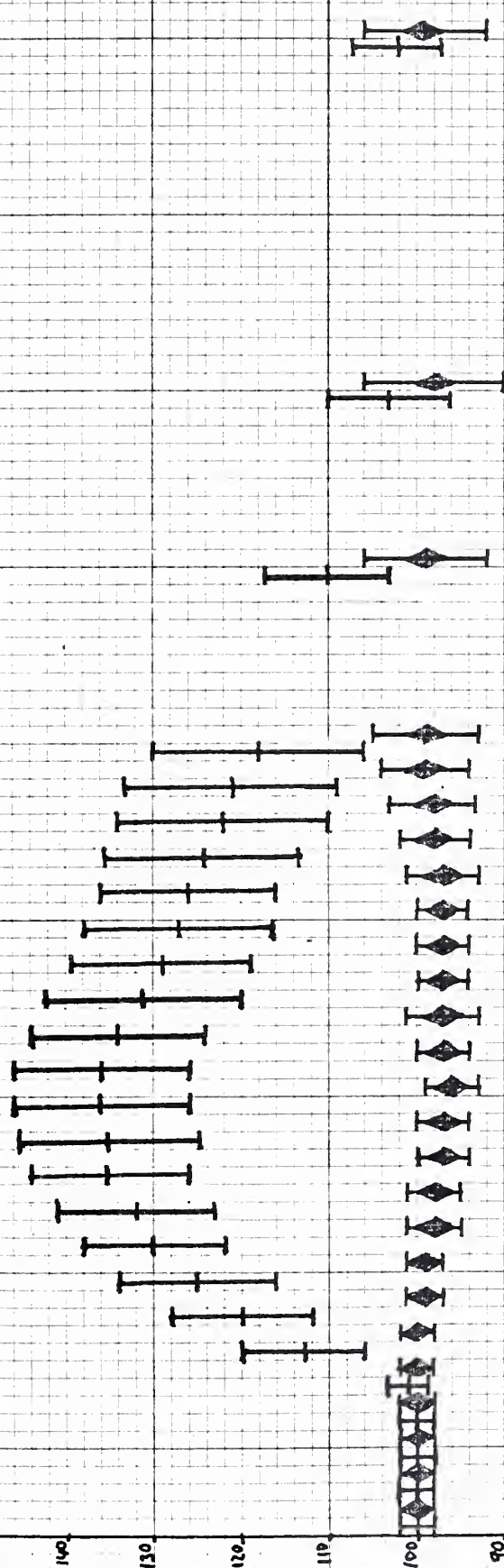
Hepatic Artery

6 Pitressin infusions
5 control infusions
Continuous
2 PU/min × 10 minutes

= NaCl Control
= Drug Effect

% of Baseline Flow

Time - Minutes

A-11
Graph #8
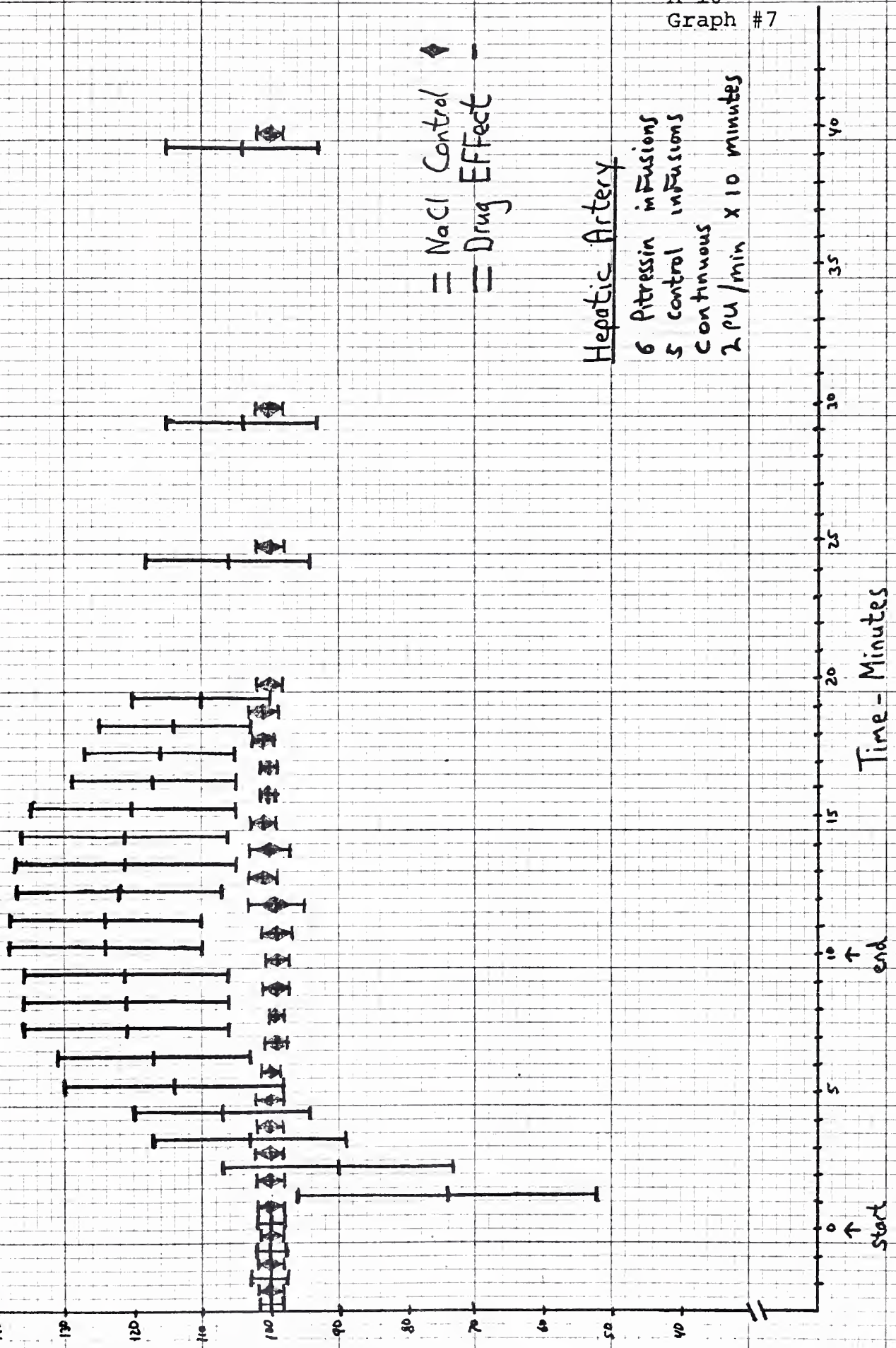
Portal Vein

6 Pitressin inFusions
5 control inFusions
continuous
2 PU/min × 10 minutes

◆ = NaCl Control
▬ = Drug Effect

% oF Baseline Flow

Time - Minutes

A-12
Graph #9

Splenic Artery

6 Pitressin infusions
5 control infusions
continuous
2 pU/min x 10 minutes

≡ NaCl Control
≡ Drug Effect

Time - Minutes

% of Baseline Flow

A-13
Graph #10

Mean Systemic Arterial Blood Pressure

= NaCl Control
= Drug Effect

6 Atressin infusions
5 control infusions
Continuous
2 Pu/min x 10 minutes

Time - Minutes

% of Baseline Blood Pressure

Start
end

A-14
Graph #11

Hepatic Artery

Sequential infusion
Continuous infusion

17 Sequential Pitressin infusions
6 continuous Pitressin infusions
2 Pu/min x 10 minutes

Time - Minutes

% of Baseline Flow

A-15
Graph #12

A-16
Graph #13
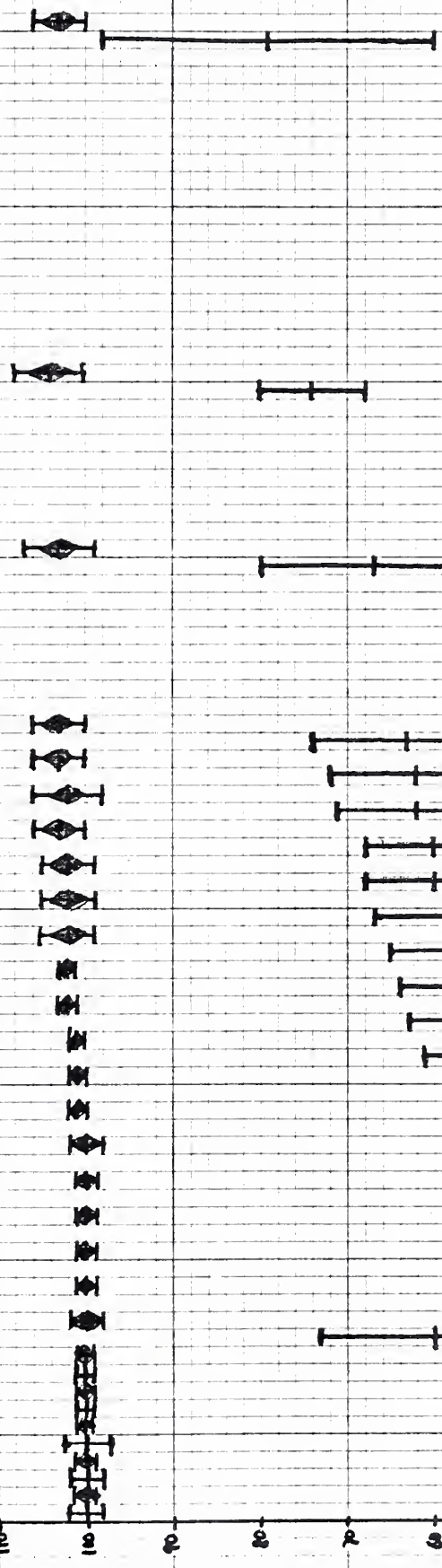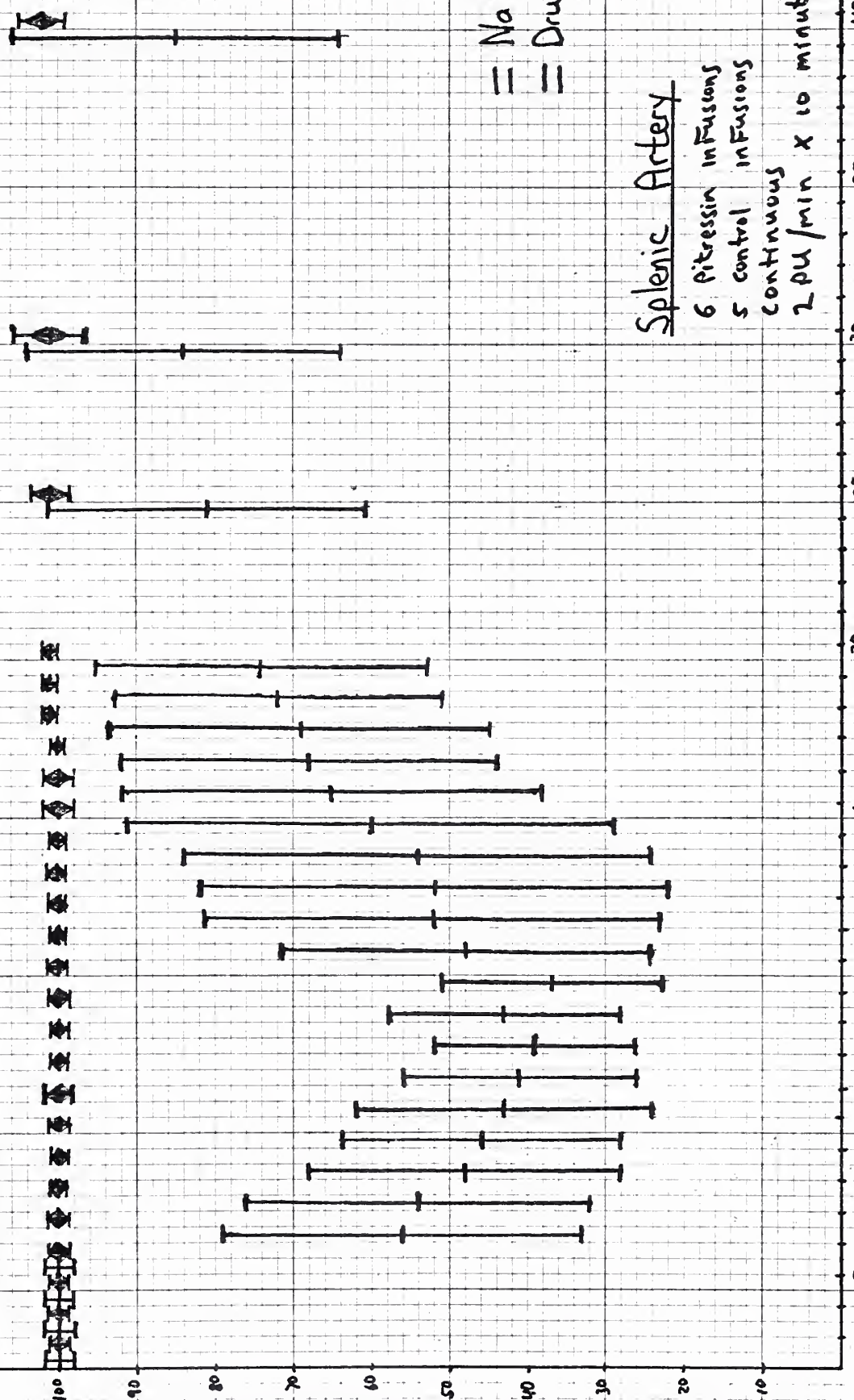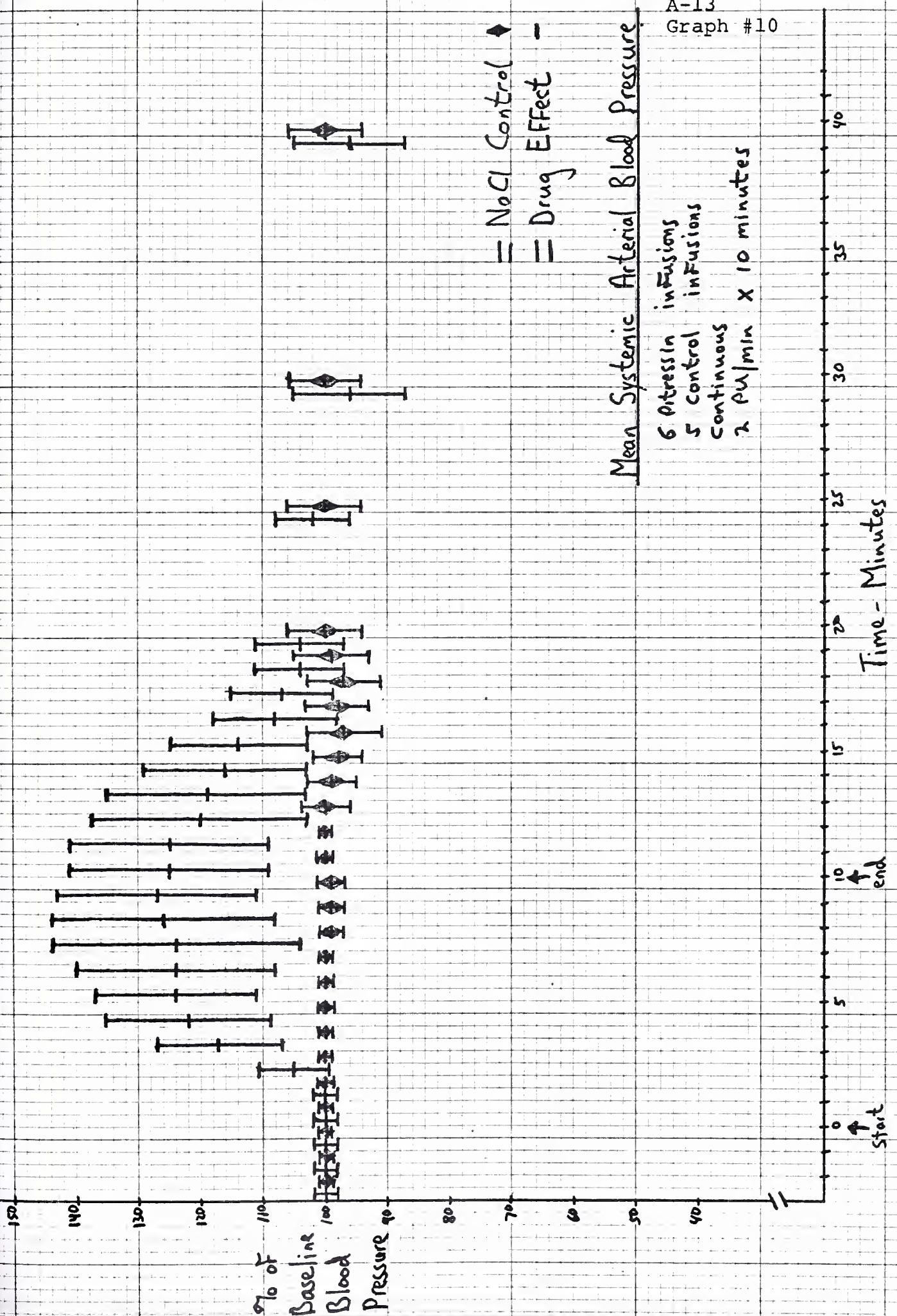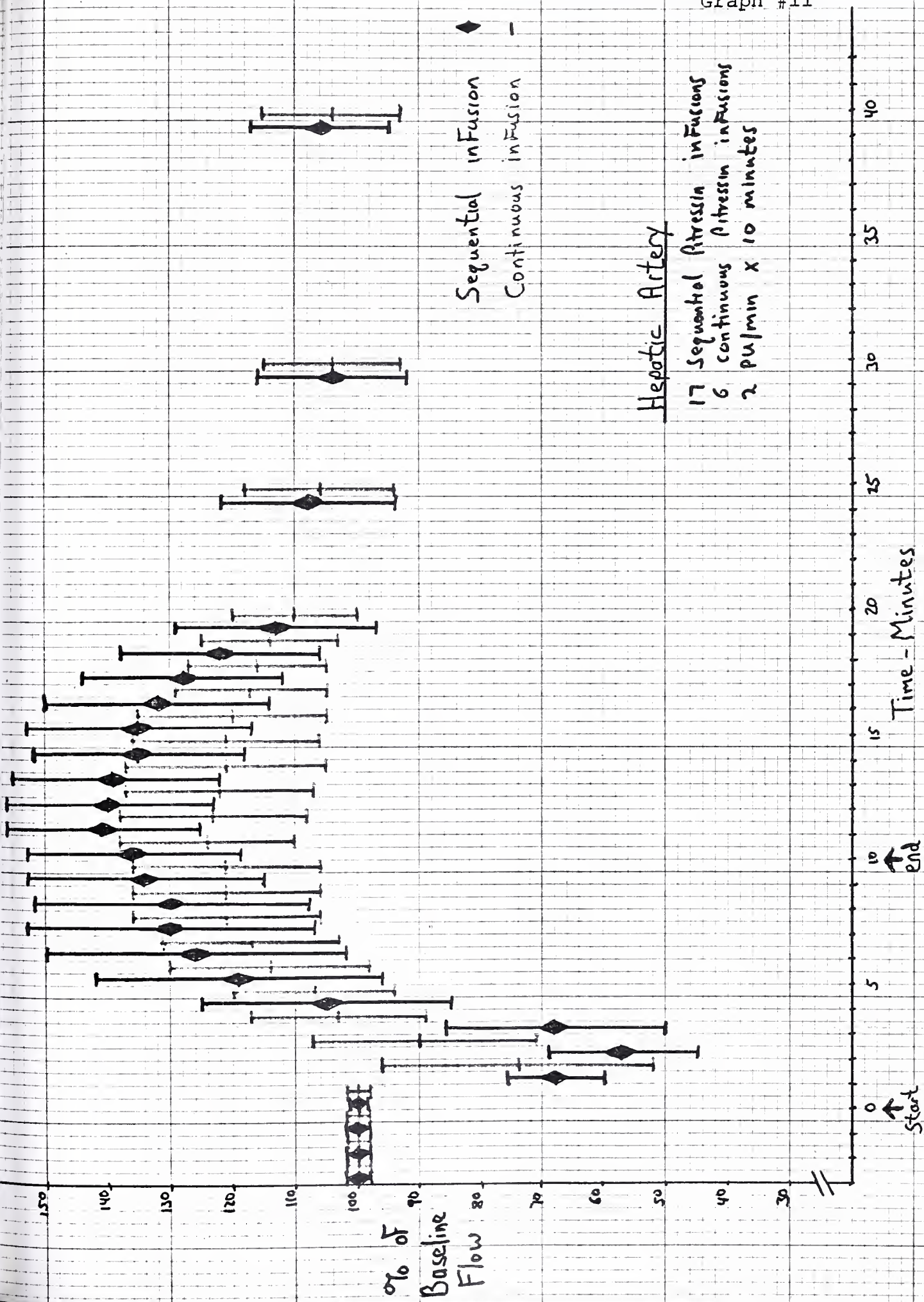
Splenic Artery

15 Sequential Pitressin Infusion
6 continuous Pitressin Infusions
2 pu/min x 10 minutes

Sequential Infusion
Continuous Infusion

Time- Minutes

% of Baseline Flow
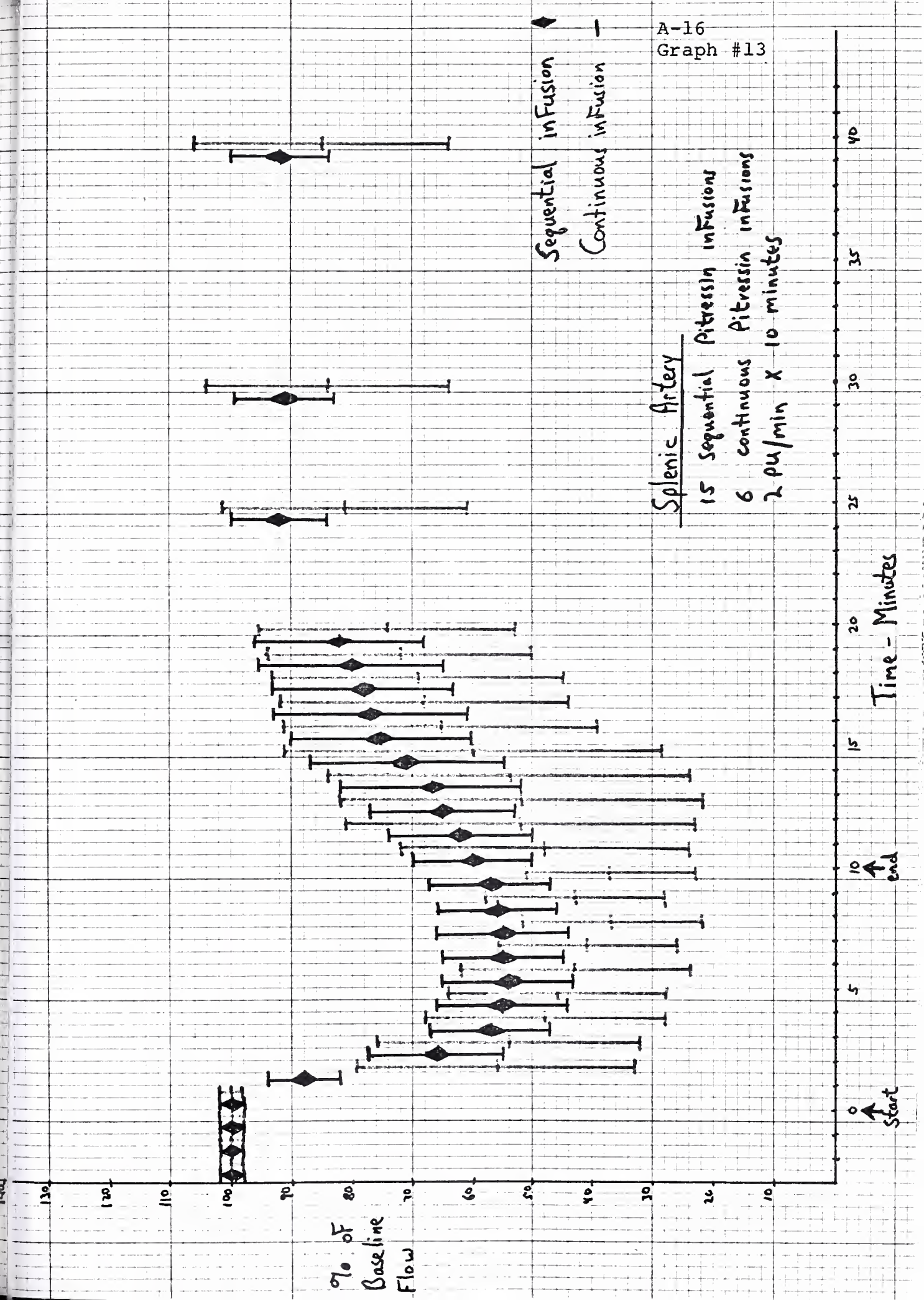
Hepatic Artery

23 Pitressin Infusions
17 control Infusions
group I c plus II A
2 PU/min X 10 minutes

◆ = NaCl Control
─ = Drug Effect

Time - Minutes

% of Baseline Flow

Portal Vein group Ic ph

A-18
Graph #15
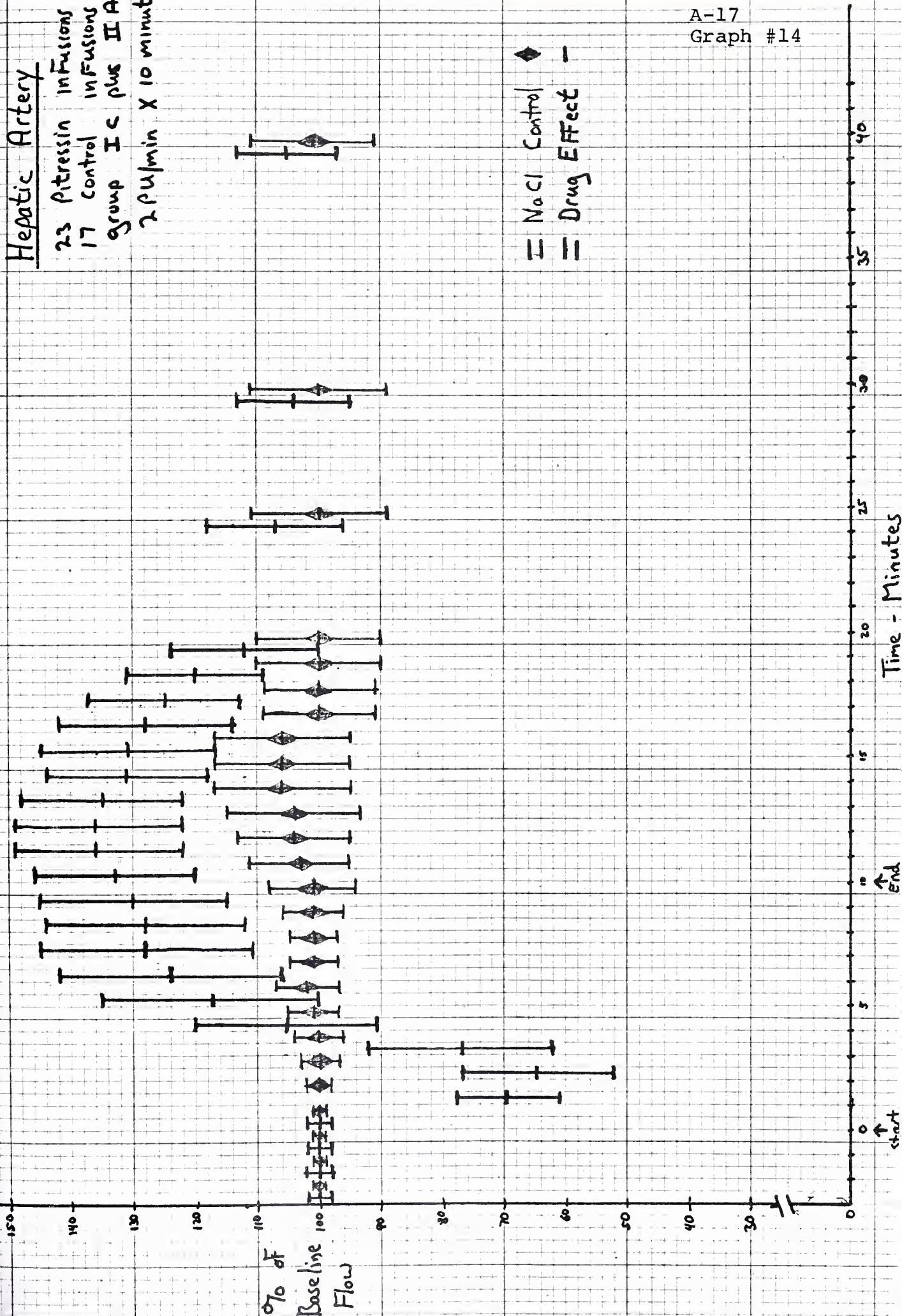
NaCl Control
Drug Effect

22 Pitressin infusions
16 control infusions
2 PU/min x 10 minutes

Time - Minutes
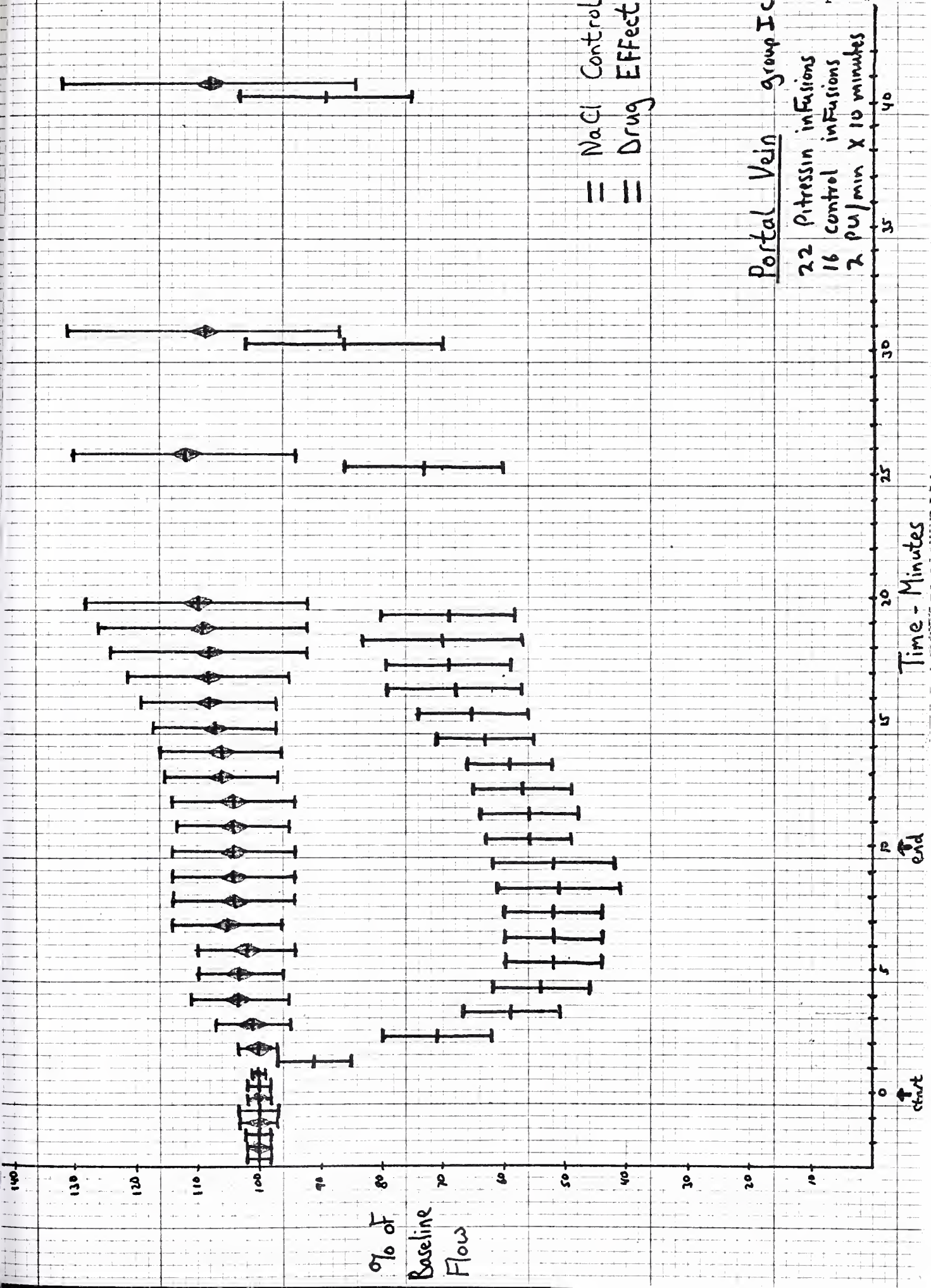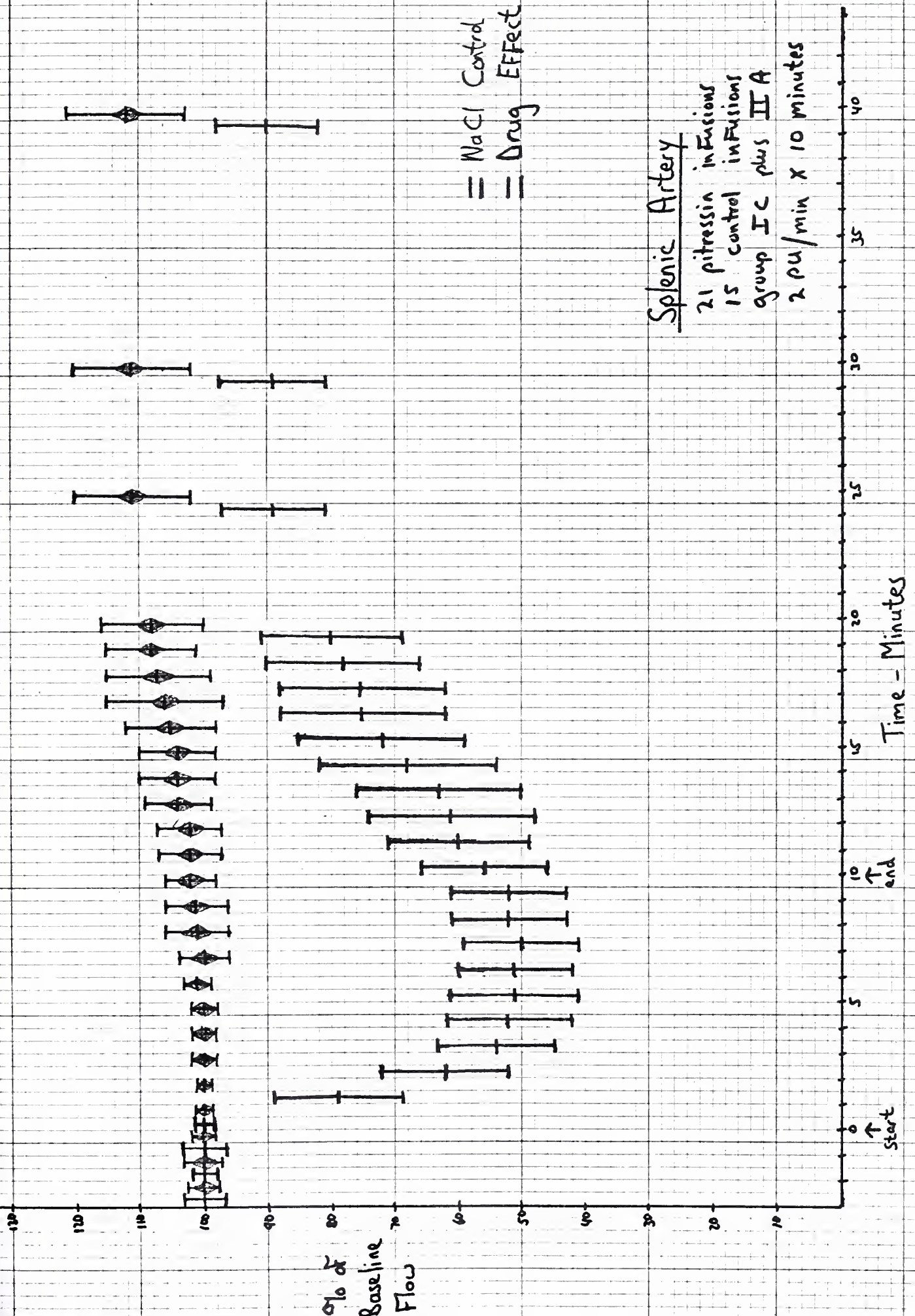
% of Baseline Flow

Splenic Artery

21 pitressin infusions
15 control infusions
group IC plus IIA
2 pu/min × 10 minutes

◆ = NaCl Control
— = Drug Effect

A-19
Graph #16

% of Baseline Flow

Time — Minutes

Mean Systemic Arterial Blood Pressure

24 Pitressin infusions
18 control infusions
group IC plus II A
2 pu/min X 10 minutes

◆ = NaCl Control
— = Drug Effect

% of Baseline Blood Pressure

Time – Minutes

Experiment #12

Pitressin, 2 PU/min
X 10 minutes

Graph #19

Hepatic Artery

5 Pitressin infusions
5 control infusions
continuous
0.2 eu/min x 60 minutes

= NaCl Control
= Drug Effect

% of Baseline Flow

Time - Minutes

Portal Vein

5 Pitressin Infusions
5 control infusions
continuous
0.2 Pu/min × 60 minutes

A-23
Graph #20

= NaCl Control
= Drug Effect

% of Baseline Flow

Time - Minutes

Graph #21

Splenic Artery

= NaCl Control
= Drug Effect

s pitressin infusions
s control infusions
continuous
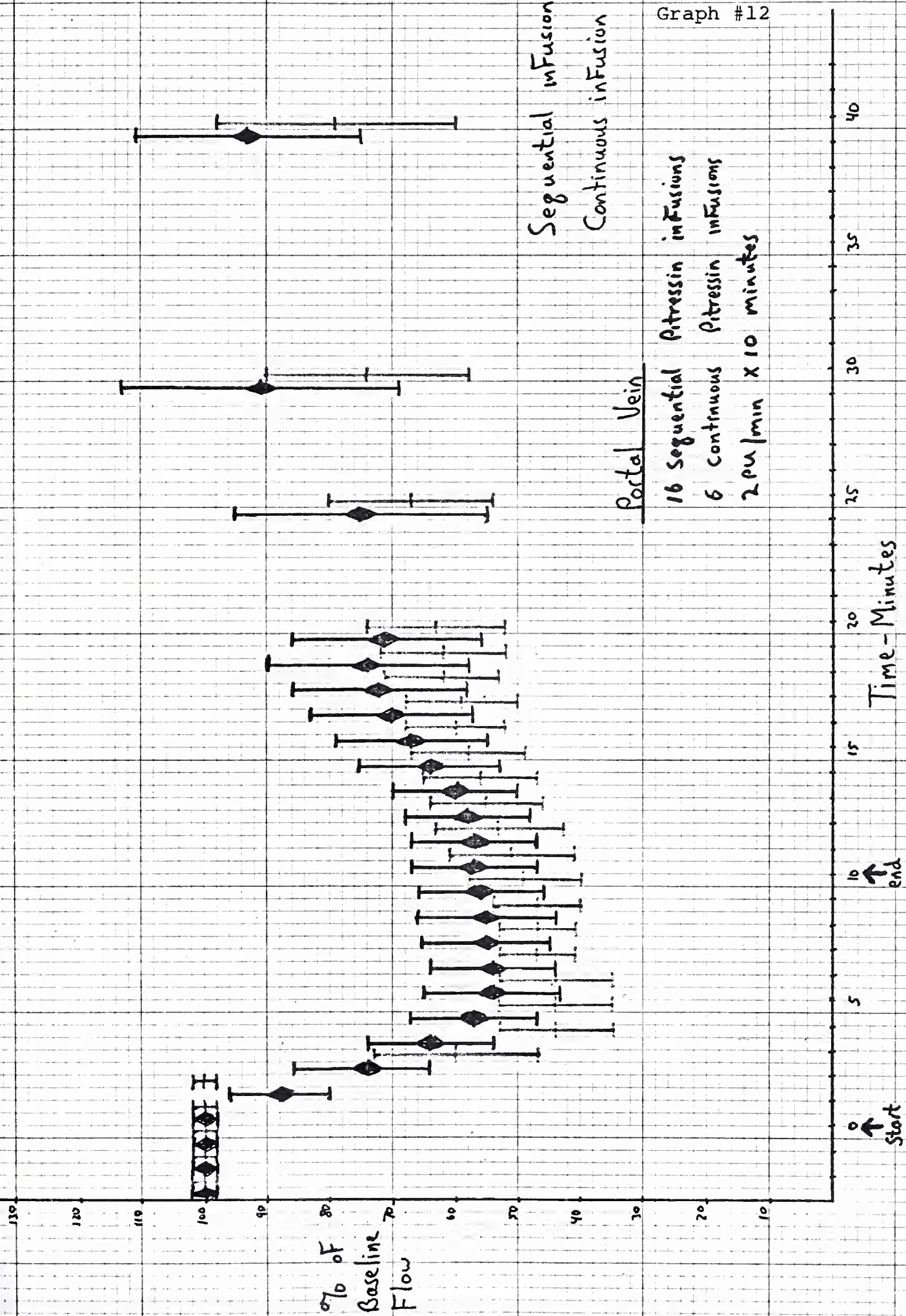0.2 pu/min. X 60 minutes

% of Baseline Flow

Time = Minutes

start   end

Graph #22

Mean Systemic Arterial Blood Pressure

＝ NaCl Control
＝ Drug Effect

5 Pitressin infusions
5 control infusions
continuous
0.2 pu/min × 60 minutes

Time - Minutes

% of Baseline Blood Pressure

start

end
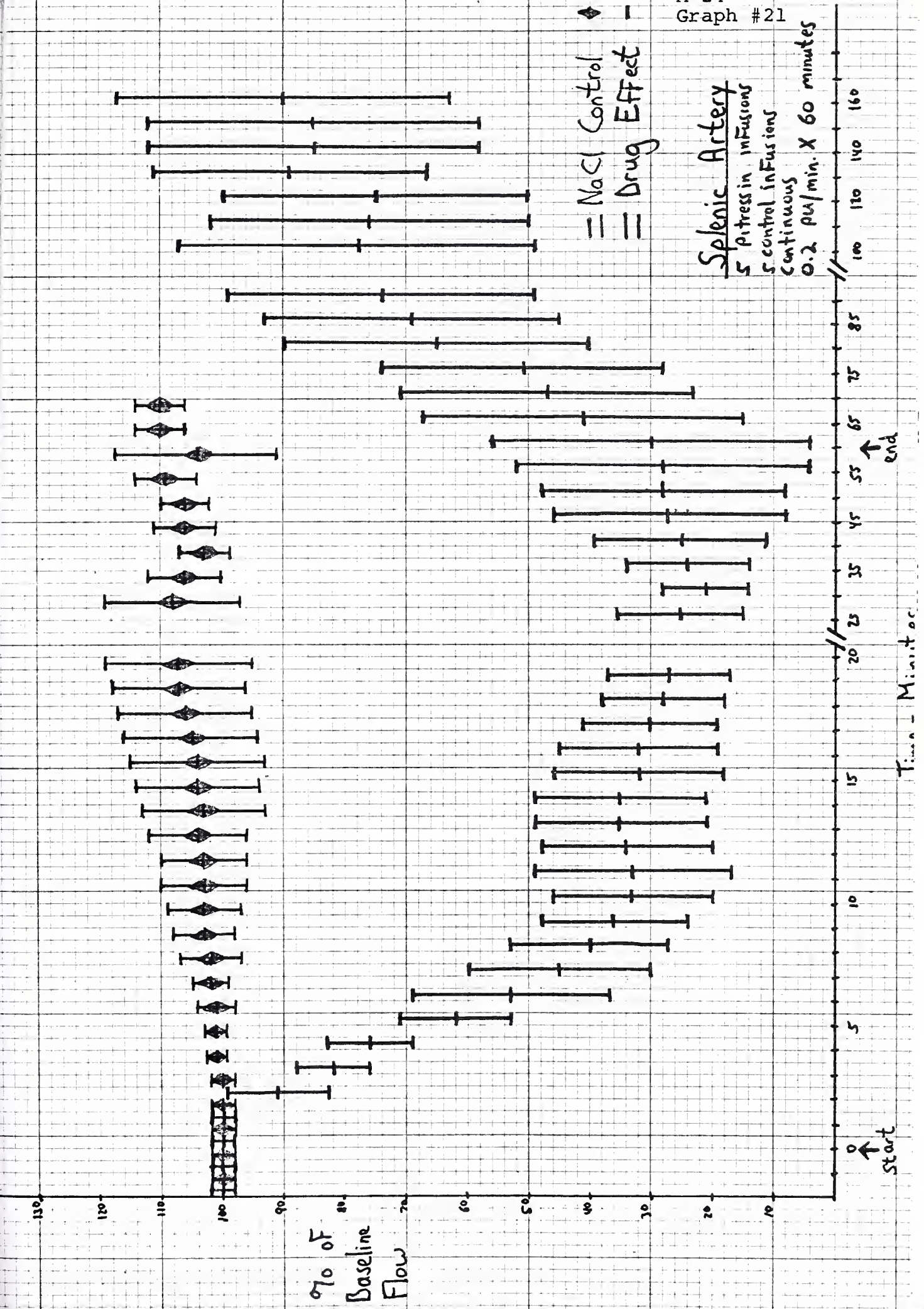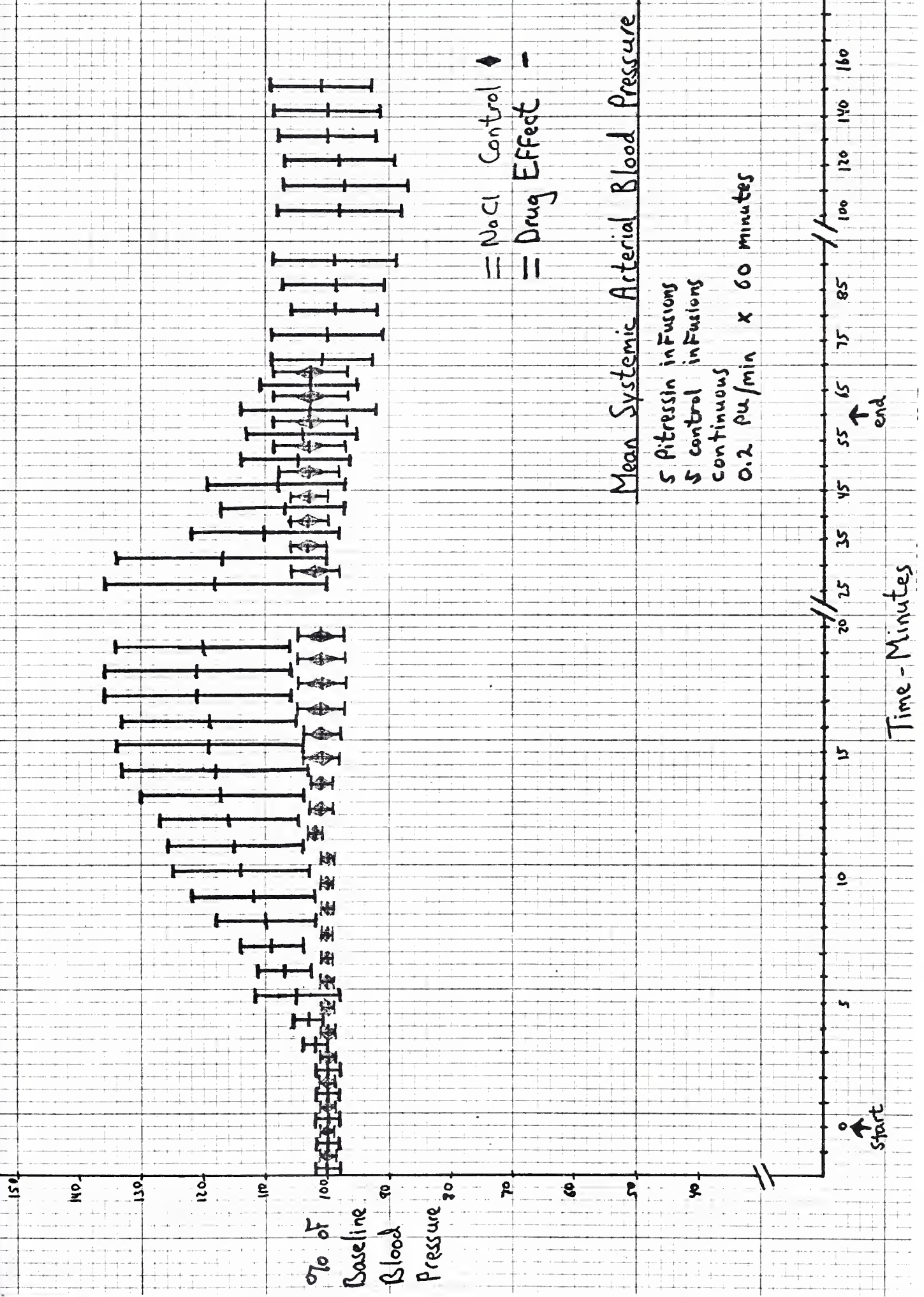
Diameter Measurements - Part II

Branches of Hepatic Artery

Left Gastric Artery

5th order branch

4th order branch

3rd order Branch

2nd order branch

1st order branch

Aorta

Celiac Axis

Splenic Artery

Gastro duodenal Artery

Superior Mesenteric Artery
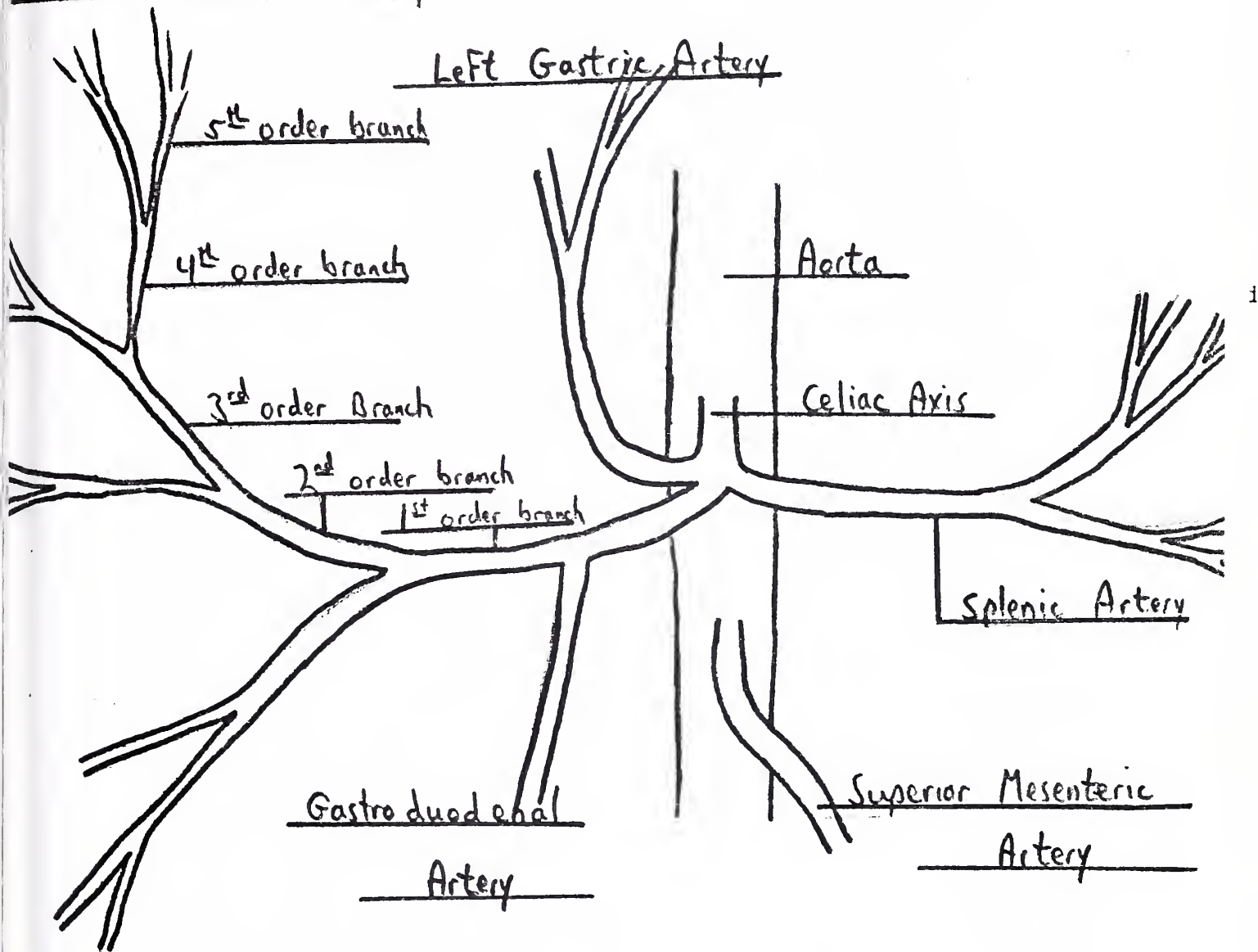
CHART #2

Part II: Vessel Diameter Changes During Intra-Celiac Pitressin Infusions
(Measured in Millimeters)

Patient #	Hepatic Artery 1st Order Pre. Post.		Hepatic Artery 2nd Order Pre. Post.		Hepatic Artery 3rd Order Pre. Post.		Hepatic Artery 4th Order Pre. Post.		Hepatic Artery 5th Order Pre. Post.		Vessels Too Small To Measure
1	7	6	4.5	4.5	2	2	2	2	1	1	No Change
2	6.5	6.5	4.8	4.8	3	3	1.5	1.5	1	1	No Change
3	5.5	5.5	4	4	3	3	1	1	No Change		
4	8	8	5.5	5.5	2.5	2.5	2	2	1	1	No Change
5	5	5	4	4	2	2	1.5	1.5	No Change		
6	8.5	8.75	7	7.5	3	3	1.5	1.5	1	1	No Change
7	8	8	6	6	4	4	3	3	2	2	No Change
8	9	9	5.5	6	2.5	3	2	2	1	1	No Change
9	7	7.5	5.5	5.5	2	2.5	1	1	No Change		
10	6	6.5	4.25	4.75	2.5	2.5	1	1	No Change		

CHART #2 — Continued

Patient #	Splenic Artery 1st Order		Splenic Artery 2nd Order		Splenic Artery 3rd Order		Splenic Artery 4th Order	
	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.
3	3.5	5.5	3.5	.2	1.5	Not Seen	1.0	Not Seen
5	7	7	3.5	2.75	2.5	1.0	1.0	Not Seen
7	5	5	4	3	1.5	1	1.0	Not Seen
9	7	7	6	4.5	4	3	2	1

Patient #	Gastric Artery 1st Order		Gastric Artery 2nd Order		Gastric Artery 3rd Order	
	Pre.	Post.	Pre.	Post.	Pre.	Post.
1	5	5.5	3.0	2.0	2.0	Not Seen

Patient #	Gastroduodenal Artery	
	Pre.	Post.
2	6	3.5
4	5	3
5	4.5	2.5
6	5	4
8	3.75	2.50
9	5	4
10	3.25	2.50

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